THE EFFECTS OF CORTICOSTERONE REPLACEMENT THERAPY ON LEVELS OF SPONTANEOUS ACTIVITY IN RATS BEARING BILATERAL VENTROMEDIAL HYPOTHALAMIC LESIONS

by

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INTRODUCTION

Spontaneous activity, particularly that of the rat, has been studied in a great many facets since the work done in the early decades of this century. It has been shown, as C.P. Richter (1927) put it, that "spontaneous activity arises from certain underlying physiological origins." Many of these underlying physiological origins have, in the past forty-eight years, been examined and reported. Any simple assumption that spontaneous activity is a function of any single factor--whether temperature, deprivation, sex, or cerebral impairment--has been proven insufficient, for spontaneous activity is brought about, in the rat, by a combination of many, many diverse variables.

One avenue of approach as to determining the regulators of spontaneous activity has been the study of those which alter the general or "normal" levels of activity--i.e., that which causes hyperactivity or hypoactivity. It is in this fashion that the present study examined its aspect of spontaneous activity.

Hetherington and Ranson (1942) performed one of the first rigorous examinations of the effects of bilateral

lesions of the ventromedial hypothalamus (VMH) upon running activity in rats. They found a sharp and nearly immediate reduction of spontaneous activity following the VMH lesions. Brooks (1946) further studied the VMH effects on running behavior, as one of several reactions to VMH lesion-induced obesity. Brooks (1946) ascertained that there is an initial hyperactive stage immediately following surgery which lasted for 12-48 hours. Following this there was a subsequent stage of quiescence with running occurring only at estrus (in females), and this occurred either regularly or irregularly. Spontaneous activity gradually decreased with increasing body weight. Later experimenters showed similar findings of decreased spontaneous activity, as measured in running wheels, following VMH lesions (Haessler and Crawford, 1967; Storlien and Albert, 1972). Sclafani(1972) also found this hypoactivity effect, but in his experiments it was shown that VMH lesions produced a "severe and permanent reduction in spontaneous wheel-running activity associated [somewhat contrary to the findings of Brooks (1946) and Hetherington and Ranson (1942)] with the loss of the female estrous activity cycle." Sclafani (1972) also sought to find the neural pathways through the VMH nuclei, the destruction of which produced the obesity and hypoactivity effects. By making certain transections he found that these effects are probably not controlled by any anterior or posterior VMH pathways, but that the effective pathways must

be certain (non-specified) bundles lateral to the VMH.

Another cause for hypoactivity in experimental rats is the removal or atrophy of the adrenal glands. Reed (1947) indicated that bilateral adrenalectomy produced a significant depression in spontaneous activity. Leshner (1971), too, showed that bilateral adrenalectomy brought on hypoactivity as a function of the activity of both the adrenal cortex and the adrenal medulla. Brittain (1973) showed that rats with (VMH lesion-induced) atrophic adrenals (especially atrophic adrenal cortices) ran significantly less than normals. With respect to this atrophic-adrenal/hypoactivity effect, it has been shown that subjects given free access to running wheels develop hypertrophic adrenals, relative to subjects confined to home cages, with no means of exercise available (Riss, Burstein, Lutz, and Johnson, 1958; Strutt and Stewart, 1970).

Richter and Uhlenhuth (1954) had hypothesized that adrenal steroids might be contributing to the production of spontaneous activity. To remedy the hypoactivity following adrenal insufficiency, glucocorticoid replacement therapy was then tested for its effects by Winter and Flataker (1960); Leshner (1971); Fuller, Chambers, and Fuller (1956), (etc.). Winter and Flataker (1960) found that adrenalectomized rats had a very difficult time carrying even small weights up a rope, in a work-performance task that the subjects had previously learned. Rats, both control and adrenalectomized subjects, were later (following

recordings of base-line work-performance quotients) given injections of either cortisone, hydrocortisone, desoxycorticosterone, or saline. It was found that two of the corticosteroids--cortisone and hydrocortisone--had considerable facilitative effects on work-performance of both the control and the adrenalectomized subjects. When all therapies were stopped it was found that controls fell back to "normal" work-performance levels, and the adrenalectomized subjects' work-performance regressed to that of post-surgical levels. Leshner (1971) found that corticosterone replacement therapy to adrenalectomized rats returned their wheel-running activity to pre-surgery levels, thus showing that a rat's level of spontaneous activity <u>is</u> dependent upon unimpaired adrenocortical functioning. Leshner (1971) concluded that "running activity serves the organism in the regulation of carcass fat levels." On these same lines Fuller, Chambers, and Fuller (1956) found that cortisone injections into adrenalectomized mice brought on a return to normal levels of spontaneous activity.

While not yet reported extensively, another, and curious, effect of VMH lesions is the concomitant atrophy of the adrenal glands (Brittain, 1973; Remley, Brittain, and Seago, 1970). What is curious here is, if the VMH lesions cause adrenocortical atrophy, and if spontaneous running-wheel activity is dependent upon both non-disconnection of ventromedial hypothalamic pathways <u>and</u> functioning adrenocortical output,

then wherein lies the ultimate causation of the decreased spontaneous activity observed following VMH lesioning? There are three alternatives. First, spontaneous activity following VMH lesioning and the accompanying adrenal insufficiency (hypoadrenality), is decreased due to too little glucocorticoid output, in turn due to adrenal atrophy. Second, spontaneous activity, following VMH lesioning and hypoadrenality, is decreased due to destruction of certain neural pathways and hypothalamic nuclei that cause a cessation of spontaneous activity directly. Third, spontaneous activity, following VMH lesioning and hypoadrenality, is controlled by something unknown. The present study considered the former two alternatives. There have been no studies in which rats bearing VMH lesions have received adrenocorticoid replacement therapy. Therefore, given corticosterone (the principal glucocorticoid in the rat) replacement therapy, VMH lesioned rats could show no change in their spontaneous activity (in which case little can be said concerning this proposed VMH-adrenal axis) or the subjects could show increased spontaneous running activity (in which case one might hypothesize that spontaneous running activity is more directly a function of adrenocortical output than has previously been imagined.)

The purpose of this study, then, was to test the hypothesis that following corticosterone replacement therapy, rats bearing bilateral ventromedial hypothalamic lesions

would exhibit levels of spontaneous running-wheel activity significantly higher than the levels they showed post-surgery, pre-therapy.

Method

Subjects. The Ss were 24 male, albino rats of the Sprague-Dawley strain, approximately 95 days of age upon receipt, and weighing between 200 and 350 grams at the start of the study. Following the initial running condition period, the Ss were randomly divided into four groups of Ss, as described below.

Apparatus. The apparatus consisted of 12 Wahmann seven-inch (wheel-radius) activity cages, and 24 Wahmann home cages. To the activity wheels were attached counters for recording each revolution run. Torque per wheel was adjusted to be approximately equal for each activity cage. The temperature was maintained at 22° C ± 1° C. All Ss were fed Purina Lab Chow, ad libitum. A David Kopf Instruments Company stereotaxic and a Qurtec CLM-2 lesion-maker were used to place the lesions and a Model 860 American Optical Company freezing-type microtome was used during histology. The Ss were run and housed under constant light conditions.

Procedure. Subjects were housed in individual home cages. There were five days of adaptation time in the wheel cages; since the later activity periods were composed of one-hour samples (as shown effective by Hitt, Gerall, and Giantonio, 1968), the adaptation periods consisted of one-hour periods each day in the wheel cages, after which the Ss were returned to their home cages. After the fifth day of adaptation

the Ss were randomly assigned six each to one of four groups, in such a way that the hourly running averages during the five days' adaptation time for each of the groups were approximately equal. The six group I Ss were to be adrenalectomized Ss; the twelve groups II and III Ss were to be bilaterally VMH-lesioned Ss; and the six group IIII Ss were to be sham-operatees (non-lesioned controls--i.e., shams).

Surgery: On days six and seven the lesions, sham-ops, (which followed the same procedure of the lesioning operation, except that no electric current was passed through the electrode, and the electrode was lowered down to, but not into the VMH), and the adrenalectomies were performed. Prior to surgery each S was given .3 cc Atrophine IP injection, followed by 1.00-1.40 cc "L.A. Thesia" anaesthetic IP.

Bilateral lesions were produced by passing 2 mA of d.c. current for 15 seconds, one second rise time, through a stereotaxically-positioned dental pin, approximately equal in size and bore to a #2 insect pin, exposed at its tip for 1 mm. An anal cathode completed the circuit. Stereotaxic coördinates used were : Lateral--.6 mm lateral to the center of the superior saggital sinus; Anterior/posterior--6.7 mm anterior of the intraaural line; Dorsoventral--8.4 mm below the top of the dura mater. The skull was placed level in the stereotaxic, as measured by same d/v readings at Llambda and Bregma.

Bilateral adrenalectomies were performed through two incisions, approximately one cm long, parallel to the spinal muscles just posterior to the last rib, and dissecting both subcutaneous muscle layers.

Activity Measures: All Ss were given three to five days recovery time in their home cages before activity measures were begun. On day 12 the Ss were again placed in the activity wheels for one hour activity periods, on any day between 11:00 A.M. and 2:00 P.M. Recordings were made of their hourly running readings. Starting on day 15 replacement therapies were begun on groups I and II Ss. These twelve Ss received 5 mg/kg body weight injections IP of .000165% corticosterone, which was suspended in steroid suspending vehicle[1.], approximately one hour prior to admission to the activity wheels. Again, recordings were made of the Ss' hour's activity readings. This replacement therapy and activity were maintained for ten days. On days 25 and 26 the Ss were sacrificed by injecting the groups I and IIII Ss with lethal doses of pentobarbital, and by passing saline, then 10% neutral buffered formalin/saline solution through the heart-circulatory system of anaesthetized groups II and III Ss. The Ss of these latter

1. Steroid suspending vehicle was provided by the Cancer Chemotherapy Nationsl Service Center of the National Institutes of Health.

two groups were then decapitated, their brains removed, and then stored in 10% formalin/saline solution.

Histology: A histological examination of the brains of the lesioned Ss was performed, in which 50-micron serial sections were cut. A Cresyl-echt violet staining procedure was followed.

Results

Surgical Results: An apparent legion of ailments attacked the Ss following surgery. As described in the Method section, four groups of Ss were originally planned. Fatalities were so numerous, however, that group III, it was decided, had to be dropped from the experiment. To obtain the needed six Ss for the group II lesioned group, eighteen rats had to be operated on. The operatees died on an average of two-to-three days following lesioning. Two other prospective lesion Ss died, one of anaesthetic shock, and one was killed, as it had no upper teeth and could not have survived long if let live. One of seven sham-lesion operatees died, and eleven operatees were needed to obtain six adrenalectomized Ss. Two autopsies were performed on the last two fatalities in the adrenalectomy Ss. It is surmised that the most likely cause of death of the lesioned and sham Ss was subdural hematoma or extensive damage to regions nearby the VMH into which the lesion expanded. No autopsies were performed on lesion fatalities. No liver, kidney, or other abdominal bleeding was seen in the adrenalectomy fatalities, and death in these Ss is most likely attributable to an inability to cope with surgical shock; the adrenalectomy fatalities occurred on an average of one-to-two days post-surgery. The attrition of Ss from each of the groups is summarized as: ten of sixteen actual lesion

operatees died; five of eleven adrenalectomy operatees died; and one of the seven sham-operatees died. The differential loss cited here is attributable only to the nature of each operation involved, and while, possibly, the groups may or may not be stocked with varyingly heartier Ss, depending on the operation's severity, this could not be controlled for, and is probably negligible in its effect on the experiment. Economy and time allowances demanded the waiver of additional operations to obtain the group III lesioned Ss.

Histological Results: Histology was performed on all six lesioned Ss' brains, and using the freezing microtome three to eight 50-micron sections of the lesioned area of each of the brains were cut and mounted. The lesions, which it had been intended would be approximately one millimeter in diameter, averaged about 1.25 mm in diameter and, consequently, spilled into adjoining nuclei. The areas partially lesioned, in addition to the VMH, were the dorsomedial hypothalamus and the periventricular nuclei in most of the Ss' brains, and also, in certain brains, the fornix, the arcuate nucleus, the reuniens nucleus, and the fasciculus mamillothalamicus. In four of the six Ss one lesion broke into the third ventricle, thus making the lesion appear larger than it was. A photomicrographic record was made of selected sections, (see Appendix II).

Activity and Statistical Results: Data were collected daily of the Ss' running-wheel revolutions run (per hour). This was done for five adaptation days, three post-surgery, base-line days, and ten replacement therapy days. These data were tabulated and averaged, and certain statistical tests were run. Table I shows the average activity per group per day, and indicates the varying activity across conditions and groups. A two-way factorial analysis of variance was run to see, generally, where any significance lay. The test yielded significant F's (at $p < .05$) in all of group, condition (i.e., adaptation, post-surgery base-line, and replacement therapy conditions), and interactive measures. Six simple analyses of variance were run to further determine where were the significantly different revolution totals; they showed: 1) There was significant variance among all adrenalectomized Ss in the three conditions ($F = 6.155$, $df = 2/15$, $p < .05$); 2) there was significant variance among all lesioned Ss in the three conditions ($F = 4.969$, $df = 2/15$, $p < .05$); 3) there was no significant variance among all shams in the three conditions ($F = .2426$, $df = 2/15$, $p < .05$); 4) there was significant variance among all adaptation time groups ($F = 8.201$, $df = 2/12$, $p < .05$); 5) there was significant variance among all post-surgery, base-line time groups ($F = 32.78$, $df = 2/6$, $p < .05$); and 6) there was significant variance among all replacement therapy time groups ($F = 114.58$, $df = 2/27$, $p < .05$). Table II shows more complete results of these analyses

of variance; from this can be seen a more accurate view of the extent of the differences among measures. A Newman-Keuls test on multiple significance comparisons was performed on all group (adrenalectomized Ss, lesioned Ss, and shams) per time (adaptation period, post-surgery base-line period, and replacement therapy period) means. The results, showing significant differences between shams, adrenalectomized Ss, and lesioned Ss during the activity conditions, are given in Table III. Figure I shows the revolutions over time of the three groups of Ss. The amount of difference varying across activity conditions is seen here, especially the lack of relative change among shams, and final lesioned Ss' activity level.

Discussion

The activity data present some rather interesting findings. Perhaps the best way to interpret the test analyses would be by looking at each group's data across activity conditions. The adrenalectomized Ss showed significant overall changes in running behavior across the adaptation time, the post-surgery, base-line time, and the replacement therapy period; this was shown in the analysis of variance. Yet, according to the Newman-Keuls test, there was no significant difference between any two of the time periods. This indicates that the adrenalectomized Ss ran differently as individual Ss during the various activity conditions, but, taken as mean activity totals, they showed no differences. The lesioned Ss showed significant differences in activity across almost all of the comparisons examined. Most importantly it was shown that the lesioned Ss had significantly different activity totals between post-surgery, base-line activity (corroborating Storlien and Albert, 1972, and Sclafani, 1971) and during replacement therapy. The corticosterone, the only variable change in these two activity conditions brought on a significant increase in activity. Not only was the activity during replacement therapy greater than during the preceding base-line period, but it was significantly higher than the activity during any period of any of the groups--notably, more than the activity, even, of the shams during

any period. The shams showed no significant differences in activity in either the analysis of variance or the Newman-Keuls test among their periods--i.e., the sham-lesion operation did not significantly alter the spontaneous activity of the shams. Across groups and through activity conditions, it was shown that there were significant differences in revolutions between both the adrenalectomized Ss and the lesioned Ss, and the shams, but not between the adrenalectomized Ss and the lesioned Ss. Also, there was no significant difference between the activity of the adrenalectomized Ss during replacement therapy and the shams then. There was, again, significance between the activity of the lesioned Ss and the activity of both of these latter two groups.

These results indicate that: 1) both adrenalectomy and VMH-lesioning produce hypoactivity; 2) corticosterone replacement therapy (using the amount suggested by Leshner (1971)--5 mg/kg body weight) brings on a return to normal activity in adrenalectomized Ss; and 3) corticosterone replacement therapy in VMH-lesioned Ss (again, using Leshner's amount) results in supranormal activity, as compared to controls (shams). There are two principal hypotheses as to why these latter two findings were obtained.

First, it may be that the activity of VMH-lesioned Ss is supranormal following glucocorticoid replacement therapy because the blood level of glucocorticoid was higher than necessary to support merely "normal" activity. This is possible

via two means. The adrenals--while atrophic--may still be secreting a basal amount of glucocorticoid which, in addition to the "normal" level of replacement therapy corticosterone, results in supranormal blood glucocorticoid levels. Alternatively, Leshner's amount of corticosterone--5 mg/kg body weight--may represent higher than normal levels, whether or not the adrenals were secreting basal amounts of glucocorticoid. If rats have supranormal levels of corticosterone, then they might exhibit such activity as that seen in this study. Leshner (1971), however, showed in previous work that surfeit amounts of glucocorticoids will not, of course, enhance spontaneous activity beyond a point.

A second hypothesis, and a much more speculative one, concerning the origin of the supranormal activity exhibited by the VMH-lesioned Ss, is that the VMH may serve, in intact rats, as a structure regulating the control of the organism's use of the adrenocorticoids--at least as they affect spontaneous activity. This may be borne out inasfar as: 1) the shams' VMH's apparently were functional and performed whatever effects they normally have on maintaining the Ss' running activity. If that normal maintenance includes regulating usage of the adrenal steroids, then this was quite possible, as the adrenals and their output were not affected by the sham operations. 2) The adrenalectomized Ss had, of course, no adrenocorticoids to maintain their spontaneous activity until corticosterone replacement therapy was begun, at which time these

Ss' intact VMH's might possibly serve to regulate usage of this incoming hormone, as they did, presumably, in the shams.
3) While it is known that certain glucocorticoids serve to maintain spontaneous activity, it is also shown here that the VMH-lesioned Ss did not only, with what is accepted as normal blood levels of glucocorticoids, run at normal levels, but they ran more than normals--these Ss have no VMH's, and if this is to be correlated with this hyperactivity, then it may be that these Ss ran more because they had no regulator of the body's uptake of the glucocorticoid. Hence the VMH may be seen as a manager of spontaneous activity through its direct control of the glucocorticoid usage.

There are a number of additional groups of Ss that might have been run during the experiment, most notably the planned group of Ss bearing VMH lesions, but receiving no corticosterone during the replacement therapy period. When this group was cut from the experiment, it was done so under the justification that it would have served only as another control group, which the shams should have been doing. They would have shown, it is supposed, continued hypoactivity during the replacement therapy period. This was shown adequately by the post-surgery, base-line data of the lesioned, group II Ss. The possible fluctuations and wheel-cue effects on activity would have been useful, however.

Other groups that might have been run include a group of

adrenalectomized and VMH-lesioned Ss, that also received glucocorticoid replacement therapy. These Ss would have shown decreased activity during the post-surgery, base-line activity condition, but their activity during the replacement therapy period would have been of particular interest. If they showed activity not significantly different from the supranormal activity of the lesioned Ss, then one might safely conjecture that the hyperactivity cannot be explained by assuming that the atrophic adrenals of the lesioned Ss were secreting some basal amount of glucocorticoid. If, on the other hand, these adrenalectomized, lesioned Ss show activity not significantly different from that of the adrenalectomized Ss during replacement therapy, then it may well be that the atrophic adrenals in lesioned Ss are secreting some amount of glucocorticoid into the blood, causing, thereby, the noticed supranormal activity. The addition of this experimental group would thus allow one to decide which of the hypotheses as to the origin of the supranormal activity of the lesioned Ss was appropriate.

A group of adrenalectomized Ss also receiving no replacement therapy might have been run. These Ss would merely have shown continued hypoactivity during the replacement therapy period, as was shown, adequately, again, by the adrenalectomized group I Ss during the post-surgery, base-line period. A group of shams receiving replacement therapy would have shown, as they would have had surfeit blood levels of corticosterone, supra-

normal activity, which is an effect already reported (Strutt and Stewart, 1970; Winter and Flataker, 1960; etc.), and unnecessary, if it can be prognosticated. Also, a group of non-operated controls might have been run, but these would have been inadequate controls. They would have had no surgical shock and recovery, both of which, it is known, affect a rat's activity.

Two additional drugs that might be administered to VMH-lesioned Ss to observe their effects, and that might further elucidate the rôle of the VMH in regulating spontaneous activity, are metopirone and ACTH (adrenocorticotrophic hormone). Metopirone is commonly used in assays for adaptive corticotroph function in the pars distalis of the hypophysis. The principal effect of metopirone, as reported in the literature, is its inhibitory reaction to corticoid synthesis in the adrenal cortex. With this effect one could, presumably, watch a S's activity as it would be following adrenalectomy, but without the actual operation. The problem with metopirone is, though, that its secondary effects include a four-fold increase in epinephrine production in the adrenal medullae, and a three-fold increase in blood-glucose levels (Parvez and Parvez, 1973; Jubiz, Meikle, West, and Tyler, 1970). While decreased glucocorticoids might cause hypoactivity, the increases in epinephrine adn blood-glucose would more than offset this, and cause, indeed, hyperactivity. ACTH might also be injected into

VMH-lesioned Ss to observe its effects on running activity. The interest in using ACTH is in its study of the VMH as a potential hypophysiotrophic area of the hypothalamus. If there were an increase in spontaneous activity following ACTH administration to VMH-lesioned Ss, the increase might be attributable to the VMH's control on CRF (corticotropin [ACTH] release factor) output, either from itself, or other hypothalamic nuclei. If there were no return to normal running following ACTH administration to lesioned Ss, then one might conclude that the VMH is not hypophysiotrophic, and/or is not involved in either direct or indirect CRF release. The problem with using ACTH lay in its irrelevancy to the stated purpose of this experiment, and in its tendency to reduce the experiment to one of merely checking to see if the VMH produces CRF or not.

The one problem encountered in the course of the experiment was the timing of the corticosterone administration. It is known that corticosterone has a half-life of only twenty minutes in circulation in the male rat (Zarrow, et al., 1964). The effects, however, of the uptake of corticosterone last longer than this 20-minute half-life. But how much longer? The effects, if the S is given normal dosage of hormone, may or may not last throughout the day. And when does the corticosterone produce its maximum action? When these questions are answered for certain, the timing of

glucocorticoid replacement therapy administration can be ascertained more reliably than by assuming that injections given one hour prior to admission to the activity wheels would be adequate.

In conclusion, it was shown in this experiment that corticosterone replacement therapy did increase spontaneous activity in VMH-lesioned rats. Not only did it increase activity, but the glucocorticoid increased spontaneous running activity to significantly supranormal levels. Two alternate hypotheses as to the origin of the supranormal activity shown by the VMH-lesioned Ss were suggested. They were: 1) that this activity was brought on by surfeit blood levels of glucocorticoids, or 2) that the VMH may be a regulator of glucocorticoid usage in intact rats, and if damaged (lesioned), might be indirectly causative of hyperactivity.

APPENDIX I

Figure I--Daily Group Running Across Time

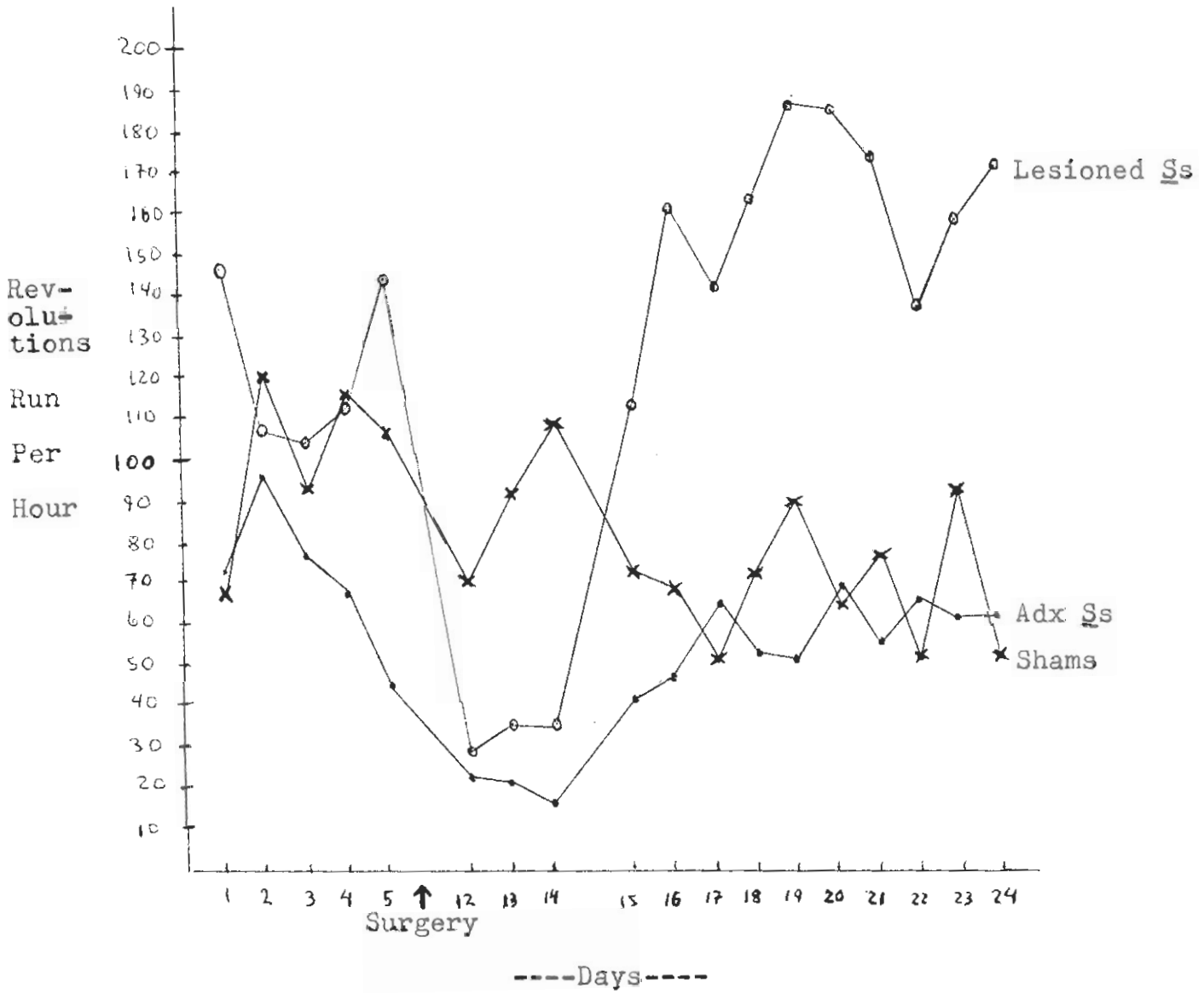


Table I--Average Running Per Group Per Day

(in revolutions per hour)

	Day	Adx Ss	Lesioned Ss	Shams
Adaptation time	1	70.8	145.8	67.0
	2	95.8	107.3	119.3
	3	67.3	110.7	113.0
	4	76.0	103.2	92.0
	5	44.2	142.5	107.0
	$\bar{X}$	70.8	121.9	99.7
Post-surgery, base-line time	1	21.3	27.5	69.0
	2	20.7	32.7	90.5
	3	16.5	31.2	107.3
	$\bar{X}$	19.5	30.5	88.9
Replacement therapy time	1	41.7	111.5	72.0
	2	45.3	259.3	67.8
	3	63.3	139.7	49.5
	4	52.0	162.5	68.7
	5	51.8	186.0	88.8
	6	66.7	182.0	63.2
	7	55.0	170.5	73.0
	8	64.8	134.0	51.7
	9	60.5	156.0	89.7
	10	60.7	170.7	52.8
	$\bar{X}$	56.2	157.3	67.3

("Adx"= Adrenalectomized)

Table II--Summaries of Analyses of Variance

(Giving overall, gross differences and all six comparisons through all three groups and all three activity conditions.)

Two-way Factorial Analysis of Variance:

	SS	df	MS	F	Sig. at $p < .05$
total	292702.55	53	5522.69	---	---
group	27668.69	2	13834.36	4.303	Sig.
condition	29555.11	2	14777.56	4.596	Sig.
cond. x group	90786.54	4	22696.64	7.059	Sig.
error	144692.21	45	3215.38	---	---

Simple Analyses of Variance:

Tested group(s) and condition(s)	df	F	Sig. at $p < .05$
1. Adx Ss, all conditions	2/15	6.155	Sig.
2. Lesioned Ss, all conditions	2/15	4.969	Sig.
3. Shams, all conditions	2/15	.2426	N.S.
4. All Ss, adaptation time	2/12	8.201	Sig.
5. All Ss, post-surg., base-line time	2/6	32.78	Sig.
6. All Ss, replacement therapy time	2/27	114.58	Sig.

Table III-Results of the Newman-Keuls Test on Multiple Significance Comparisons

(Giving all 36 possible comparisons among the nine condition/groups)

	Adx-PS 19.5	Les-PS 30.5	Adx-RT 56.2	Sham-RT 67.3	Adx-A 70.8	Sham-PS 88.9	Sham-A 99.7	Les-A 121.9	Les-RT 157.3
Adx-PS 19.5				*		*	*	*	*
Les-PS 30.5			*			*	*	*	*
Adx-RT 56.2								*	*
Sham-RT 67.3								*	*
Adx-A 70.8						*		*	*
Sham-PS 88.9									*
Sham-A 99.7								*	*
Les-A 121.9									*
Les-RT 157.3									

(Key: "Adx"= adrenalectomized Ss; "Les"= lesioned Ss; "A"= during adaptation period; "PS"= during Post-surgery, base-line period; "RT"= during the replacement therapy period.

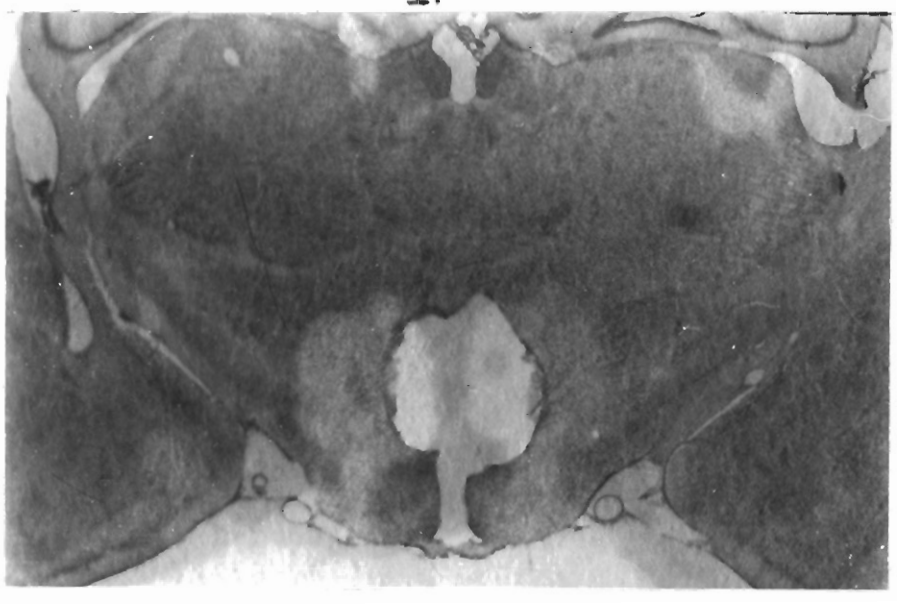
All figures represent average group revolutions per hour.

*= a significant difference between measures, at $p < .05$.)

APPENDIX II

The following are photomicrographs of three brain sections. In the lower center of each is one or two white area(s)--these are the lesions. Picture I is from S # 41, and represents the maximum damage done to any brain. Picture II, from S # 29, and picture III, from S # 12, are representative of typical lesions. They both contain one lesion that broke into the third ventricle, thus making the lesion on the right, in both pictures, appear larger than it actually was.

I.



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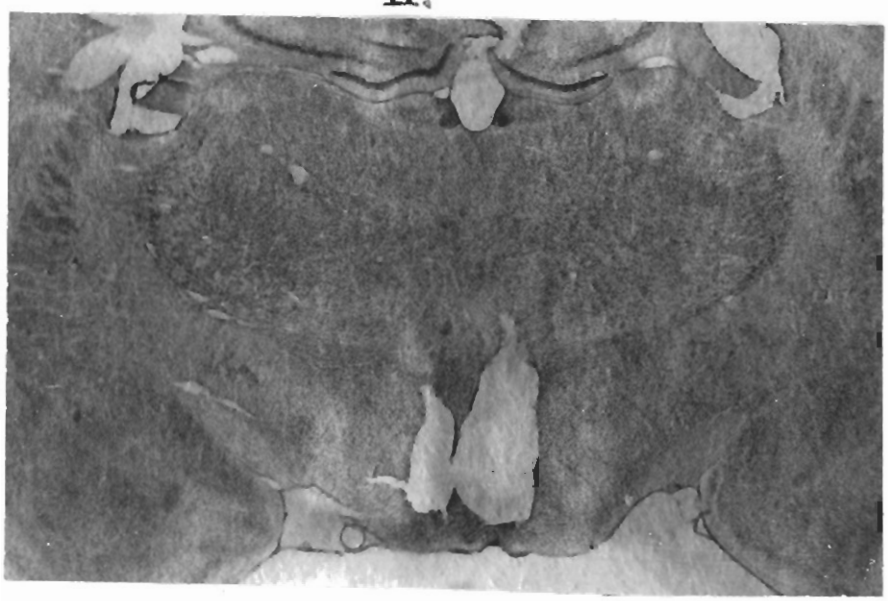

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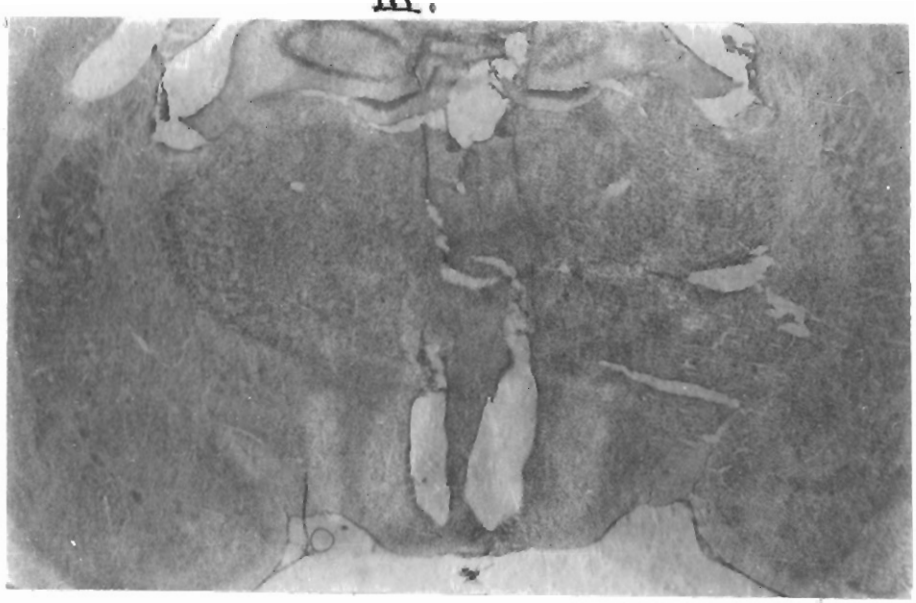

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