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# The influence of ovarian hormones on the recovery period following lateral hypothalamic lesions.

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THE INFLUENCE OF OVARIAN HORMONES ON THE RECOVERY PERIOD  
FOLLOWING LATERAL HYPOTHALAMIC LESIONS

A Thesis Presented  
by  
Lindy E. Harrell

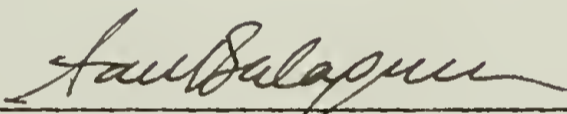
Submitted to the Graduate School of the  
University of Massachusetts in  
partial fulfillment of the requirements for the degree of

MASTER OF SCIENCE  
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Major Subject: Psychology

THE INFLUENCE OF OVARIAN HORMONES ON THE RECOVERY PERIOD  
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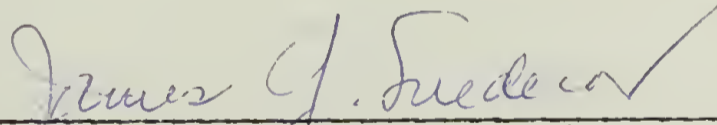
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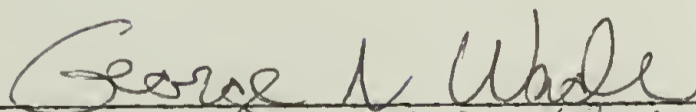
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Saul Balagura, M.D., Ph.D. (Chair-  
man of Committee)



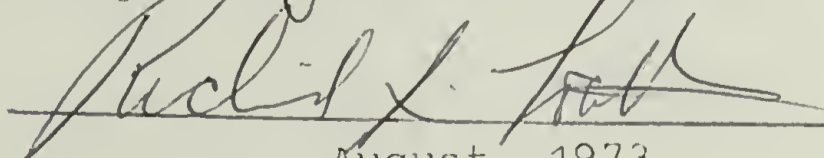
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August, 1973

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Following bilateral lesions of the lateral hypothalamus animals are rendered completely aphagic and adipsic (Anand and Brobeck, 1951; Teitelbaum and Stellar, 1954). If not maintained by intragastric feeding, rats will eventually die of starvation and dehydration. However, if the animals are kept alive a gradual recovery of food and water intake will occur. This recovery period has been extensively and carefully studied, and four distinct recovery stages have been identified (Teitelbaum, 1961; Teitelbaum and Epstein, 1962). The first stage of recovery is characterized by the animal's refusal of all food and water. In the second stage wet and palatable foods are accepted, although not in sufficient quantities to maintain life. During the third phase, the animal is able to regulate its caloric intake on wet and palatable foods, but is unable to regulate its weight on dry food. Finally, in the fourth stage the lateral hypothalamic lesioned animal will accept dry food and water in sufficient amounts to maintain life.

For quite sometime, it was assumed that this recovery period was unmodifiable. Recently, however, it was found that maintaining animals at reduced body weight prior to lateral hypothalamic lesions shortened the recovery (Powley and Keesey, 1970). It was postulated that lesions of the lateral hypothalamus result in a lowering of the set-point for weight regulation, and that the normal interruption of feeding following such lesions is the consequence of an



effort by the animal to bring its body weight into balance with this new level of regulation.

Modification of the recovery period may also result by altering brain norepinephrine, which has been hypothesized to be a neurotransmitter in the mediation of feeding behavior (Grossman, 1960; Berger, Wise, and Stein, 1971). Systemic injections, three days prior to placement of lateral hypothalamis lesions, of  $\alpha$ -methyl-p-tyrosine, which reduces brain norepinephrine, shortens the length of the recovery period, probably as a result of a denervation super-sensitivity (Glick, Greenstein, and Zimmerberg, 1972). Similarly, administration of the pancreatic glucodynamic hormones, insulin and glucagon, five days prior to surgery shortens or lengthens, respectively, the recovery period (Balagura, Harrell, and Ralph, 1973). It was postulated that these two hormones altered this period by affecting norepinephrine synthesis. Thus, various pre-surgical manipulations have been found to modify the recovery period following lateral hypothalamic lesions.

The gonadal hormones, estradiol and progesterone in the female and testosterone in the male, have been implicated in food intake and body weight regulation. Male rats show negligible day-to-day fluctuations in both food intake and hormonal levels (Wade, 1972). Castration of adult male rats causes a slight reduction in weight gain and food intake, which is reversible by replacement with testosterone (Bell and

Zucker, 1971; Kakolewski, Cox, and Valenstein, 1968). Female rats show marked variations in body weight and food intake, which correlate with the estrous cycle. During proestrus, when estrogen levels are high relative to those of progesterone (Hashimoto, Henricks, Anderson, and Melampy, 1968; Yoshinaga, Hawkins, and Stocker, 1969), both food intake and body weight decrease (Brobeck, Wheatland, and Strominger, 1947), while at diestrus, when progesterone levels are high relative to those of the estrogens (Hashimoto, Henricks, Anderson, and Melampy, 1968; Yoshinaga, Hawkins, and Stocker, 1969), body weight and food intake increase. Thus, body weight and food intake in the female rat seem to be influenced by the relative levels of these two hormones.

Ovariectomy, which eliminates progesterone and estrogen, increases both food intake and body weight (Wade, 1972). Replacement therapy with estradiol restores pre-operative levels of both food intake and body weight (Tarttelin and Gorski, 1971), while treatment with progesterone does not influence either food intake or body weight in the ovariectomized animal. Therefore, estradiol appears to be the main ovarian steroid regulating body weight and food intake in the female rat.

It has been postulated that the estrogens may act upon hypothalamic mechanisms to regulate body weight and food intake. Since the ventromedial and lateral hypothalamic areas seem to be involved in the neural mediation of feeding

(Stellar, 1954), unilateral implants of estradiol benzoate were placed in these regions (Wade and Zucker, 1970). The estradiol implants in the ventromedial hypothalamus were found to decrease food intake, while the implants in the lateral hypothalamus had no effect. Thus the estrogens may act through the ventromedial hypothalamus in the adult female rat to restrain food intake.

Since food intake appears to be regulated jointly by the lateral and ventromedial hypothalamus, and the ventromedial hypothalamus is thought to influence food intake by inhibiting the lateral hypothalamus (Teitelbaum and Epstein, 1962), estrogens may exert an indirect effect on the lateral hypothalamus. If this is the case, ovariectomy or the lack of estrogens may affect the recovery period following lateral hypothalamic lesions. The present research was designed to investigate the relationship between estrogens and the length of the recovery period following lateral hypothalamic lesions. Since body weight is closely linked to both estrogens and the modification of lateral hypothalamic recovery, the interactions of estrogens and body weight upon this recovery period were also examined.

#### METHOD

Thirty-six female rats of Charles River strain, weighing between 220-260 grams, were housed individually in a temperature controlled room ( $72^{\circ}\text{F} \pm 2$ ). Illumination was provided by standard fluorescent ceiling lights (On at 6 am, Off at

8 pm).

Adaptation and Experimental Procedure: To permit the rats to adapt to the colony and to obtain information on individual body weight and 24 hour food intake, the rats were given five days of adaptation with food and water ad libitum. Food consumption and body weight measurements were taken daily at 7 am.

Following the adaptation period, 18 of the rats underwent ovariectomy, while 18 underwent laparotomy but not ovariectomy (sham controls). When all the animals had recovered to their pre-operative weight, they were assigned to one of six groups: normal weight-sham (NW-S), normal weight-ovariectomized (NW-O), underweight-sham (UW-S), underweight-ovariectomized (UW-O), overweight-sham (OW-S), and overweight-ovariectomized (OW-O).

The NW-O group was pair-fed with the NW-S group, which was placed on an ad libitum feeding schedule. This was done so that the body weight of the NW-O group was approximately that of the NW-S group. The UW-S and UW-O were reduced to 80% of normal weight groups' body weight by restricted feeding. The OW-O group was given food ad libitum, while the OW-S group was given daily injections of progesterone (PG. 1.0 mg/rat) and insulin (Semilente 8U/rat) to induce hyperphagia and obesity.

When all animals reached their body weight criterion, i.e. normal weight for the NW-S and its pair-fed group NW-O,

80% for the UW-S and UW-O, and 120% for the OW-S and OW-O groups, all drug treatments were discontinued. Five days later all animals received bilateral hypothalamic lesions. These lesions were made under Nembutal anesthesia (40 mg/kg), with the aid of a stereotaxic instrument, by passing anodal current of 1mA for 20 seconds through an insulex coated, 0.2mm in diameter stainless steel electrode exposed 0.5mm at the tip. The stereotaxic coordinates, with the animal's skull in the horizontal position were 5.8mm anterior to the inter-aural line, 2.0mm lateral to the midsaggital line, and 7.5mm below the dorsal surface of the cortex. After surgery the rats were returned to their cages and their feeding behavior observed. If an animal had not recovered eating behavior within two days, intragastric feeding (5ml, 3 times daily) of milk was commenced. Following recovery of eating and stabilization of body weight, the animals were sacrificed, their brains removed, sliced in sections 60 $\mu$  thick, and stained with cresylecht-violet for histological verification of the lesion placement.

## RESULTS

Following lateral hypothalamic lesions all the animals showed the characteristic aphagia. However, the length of time to recovery, which was defined in this case as Teitelbaum's Stage 3, depended upon the pre-treatment the animal had received. Figure 1 summarizes the results obtained. The UW-S and UW-O groups recovered the fastest, 0.33 and 0.66

days respectively. A t-test revealed that there was no difference in recovery time between these two groups. The NW-S and NW-O groups recovered in 3.8 and 1.6 days respectively ( $p < 0.05$ , 2-tailed t-test). The OW-S and OW-O groups recovered in 5.8 and 3.0 days respectively ( $p < 0.02$ ).

A comparison among the three ovariectomized groups revealed that the UW-O group recovered faster than the NW-O group ( $p < 0.05$ ), and that the latter in turn recovered faster than the OW-O group ( $p < 0.05$ ). The animals with ovaries showed a similar pattern, with the UW-S group recovering faster than the NW-S group ( $p < 0.002$ ), which in turn recovered faster than the OW-S group ( $p < 0.05$ ). A t-test between the two groups that were allowed ad libitum food, i.e., the OW-O and NW-S groups, revealed no significant difference in recovery time between them.

An analysis of variance indicated significant differences between the body weight of the non-ovariectomized and the ovariectomized groups ( $f=11.2$ ,  $df=1,30$ ,  $p < 0.005$ ). A comparison of groups on the 35<sup>th</sup> day after lesioning failed to show any significant differences in body weights among the three ovariectomized groups. In the normal groups, a significant difference in body weight was found for only one comparison, that between the NW-S and the OW-S groups ( $p < 0.001$ , 2-tailed t-test). Comparisons between individual groups showed a statistical difference between the NW-S and all ovariectomized groups ( $p < 0.001$ ), between the UW-S and

all ovariectomized groups ( $p < 0.001$ ), and between OW-S and the OW-O and NW-O groups ( $p < 0.001$ ). (See Figure 2).

Figure 3 depicts the maximum weight loss after lateral hypothalamic lesions. Since there were no significant differences between the ovariectomized and the sham groups across each weight category their data were combined. The underweight animals lost the least amount and the overweight animals the greatest amount of weight. It is also interesting to note that all the animals except the underweight groups lost a significant ( $p < 0.001$ ) amount of weight after lateral hypothalamic lesioning when compared with their pre-operative baseline.

An analysis of variance of the food intake yielded similar results to those found in the case of body weight. Significant differences were found between the ovariectomized and non-ovariectomized groups ( $F=26.2$ ,  $df=1,30$ ,  $p < 0.0001$ ). A comparison on the 35<sup>th</sup> day showed there were no statistical differences in food intake either within the ovariectomized or the non-ovariectomized groups. Comparisons between individual groups showed a significant difference between the NW-S and all ovariectomized groups ( $p < 0.001$ ), between the OW-S and all ovariectomized groups ( $p < 0.001$ ), and between the UW-S and the UW-O and OW-O groups ( $p < 0.001$ ). (See Figure 4).

Histology: Histology revealed that in every case the lesion encompassed bilaterally the lateral hypothalamus-medial

forebrain bundle area, as well as the most medial edge of the internal capsule at the level of the ventromedial hypothalamus (see Figure 5).

#### DISCUSSION

The results of this study seem to indicate that the lack of ovarian estrogens somehow modifies the recovery period following lateral hypothalamic lesions. It is also clear that this modification is not just due to their effects on absolute body weight. For if this had been the case the OW-O animals would have been expected to recover in the same amount of time as the OW-S animals. The same would have also been the case for the NW-S and NW-O rats. Therefore, the estrogens or the lack of them must be altering this recovery period in an entirely different manner. In recent research (Tarttelin and Gorski, 1971; Mook, Kenney, Roberts, Nussbaum, and Rodier, 1972; Redick, Nussbaum, and Mook, 1973) it has been found that estradiol exerts control over body weight in a manner consistent with the hypothesis that the estrogens may control a regulatory body weight set-point. Hence, overweight ovariectomized animals given replacement therapy with estradiol restrict their food intake until they return to normal body weight. Once at this point, food intake rises to a normal level, but body weight remains constant. In the case of the ovariectomized rat, in which replacement therapy is not given, body weight rises to a new level and then becomes stable. This suggests that the animal is actually regulating its body



weight only at a higher level. Perhaps, this is very similar to what happens following ventromedial hypothalamic lesions, when the regulatory body weight set-point is shifted in an upward fashion (Hoebel and Teitelbaum, 1966).

Consequently set-point is more likely the important variable than absolute body weight in influencing lateral hypothalamic recovery, as has been indicated previously (Powley and Keeseey, 1971). Our results support this contention. The OW-O animals, which are at set-point even though they are obese, recovered in approximately the same amount of time as the NW-S animals, which of course were at set-point.

Since lateral hypothalamic lesions have been hypothesized to shift body weight set-point in a downward direction (Powley and Keeseey, 1971), it is not surprising that the animals, which were originally under their own set-point recover faster than animals at set-point. Thus both the NW-O and UW-O animals resumed eating behavior more quickly than did the OW-O group. More interestingly, however, is the fact that the UW-O animals recovered faster than the NW-O group. This could arise because the UW-O animals are further below set-point than the NW-O animals.

From the data presented on the animals with intact ovaries (UW-S, NW-S, OW-S) it is easily seen that deviations from the set-point which is represented by the animal's body weight, have striking effects on the recovery period. The further the animal is above its original set-point the longer it takes

for the animal to resume eating, while the further the animal is below set-point the quicker she recovers.

Thus it can be seen from a comparison of the pre-operative body weight (Figure 2) and the length of time to recovery (Figure 1) that the absolute weight of the animal is unimportant for the recovery of eating behavior following lateral hypothalamic lesions. Of more importance is the relationship between the animal's weight and its own body weight set-point.

A significant increase in the anterior hypothalamus (Donoso and Stefano, 1965) and an increased turnover rate in the hypothalamus (Anton-Tay and Wurtman, 1968) of norepinephrine have been found following ovariectomy. A reduction of this norepinephrine has been found to occur following injections of estradiol (Donoso and Stefano, 1965; Donoso, Stefano, Biscardi, and Cukier, 1967). Furthermore, it has been suggested that the circulating levels of estradiol may have a regulatory influence on norepinephrine elicited eating (Simpson, 1970). With these facts in mind, it might in turn be postulated that estradiol controls body weight set point by influencing the levels of circulating norepinephrine. However, more research into the relationship between norepinephrine and body-weight set-point will be necessary.

Despite the fact that body weight set-point influences the time to recovery it seems to have very little to do with the amount of weight loss after a lateral hypothalamic lesion. This phenomena instead appears to depend on the absolute body

weight of the animal. Thus irrespective of ovarian function, obese animals lose more weight than non-obese animals after lateral hypothalamic lesions. The time of maximum weight loss, however, is not necessarily the same between animals of similar weights but differing ovarian condition. Thus, the OW-O animals' maximum weight loss occurred 6 days after surgery, while that of the OW-S animals occurred at 8 days.

By the 35<sup>th</sup> day after lesioning, all the ovariectomized animals weighed approximately the same. They, also, were heavier and consumed more food than did the non-ovariectomized groups. The elevated body weight was not unexpected (Wade, 1972). However, the increased food consumption found conflicts with some of the newer literature (Mook et al., 1972; Tarttelin and Gorski, 1971). Perhaps food intake would have returned to normal levels if the study had been run longer.

It is interesting to note that all the animals with ovaries, except the OW-S group, returned to their pre-operative body weight. This result conflicts with previous findings (Powley and Keeseey, 1970), which demonstrated that following lateral hypothalamic lesions male rats do not return to their pre-operative body weight. However, the results are in agreement with a later study, which showed that lateral hypothalamic lesions do not affect the return to pre-operative body weight in female rats (Cox and Kakolewski, 1970). Whether the OW-S group did not return to its original body weight set-point because of the pre-operative drug treatment or because

obesity, itself, has the ability to shift the regulatory body weight set-point is unknown.

Summarizing the main findings of my research, the severity and length of aphagia following lateral hypothalamic lesions are dependent upon two separate components in the body weight regulatory processes. First, body weight immediately prior to the lateral hypothalamic lesion determines the amount of weight loss. Second, body weight set-point, which is not always reflected by the actual body weight of the animal, determines the length of the recovery period.

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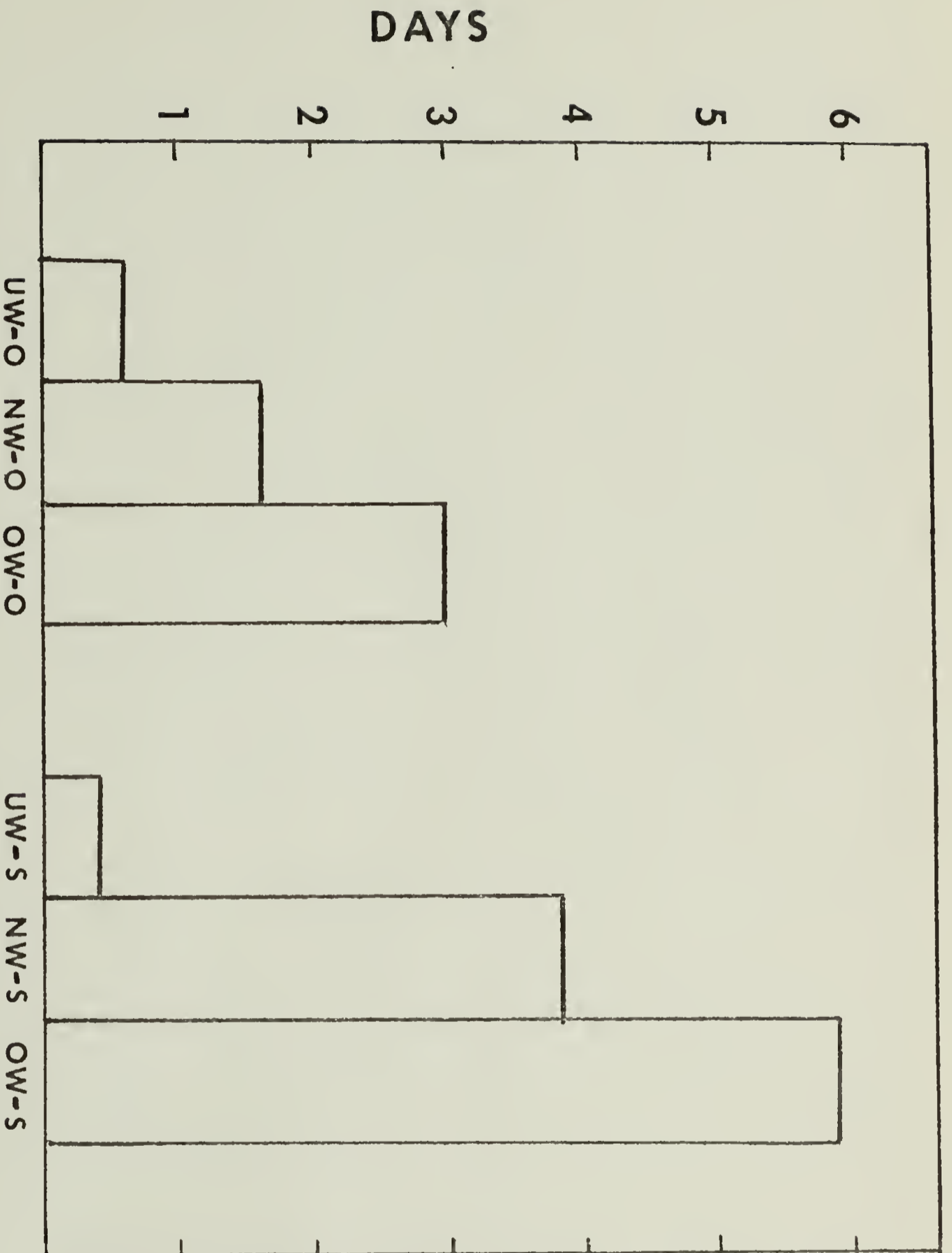
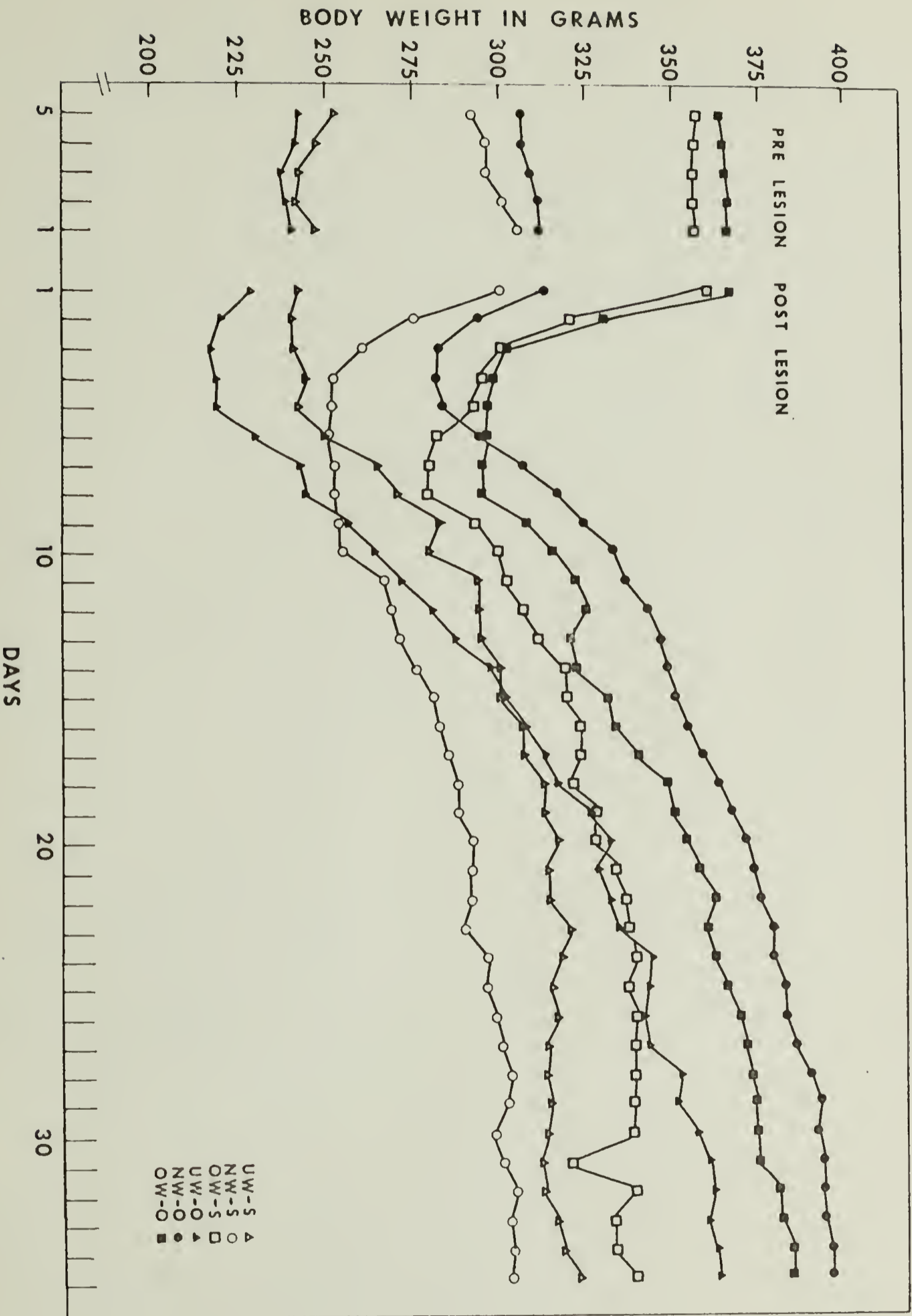


Figure 1. Summarizes the mean time of recovery following lateral hypothalamic lesions, Recovery was defined as Teitelbaum's Stage 3.



Figure 2. Mean daily body weights five days prior to and thirty-five days after lateral hypothalamic lesions.



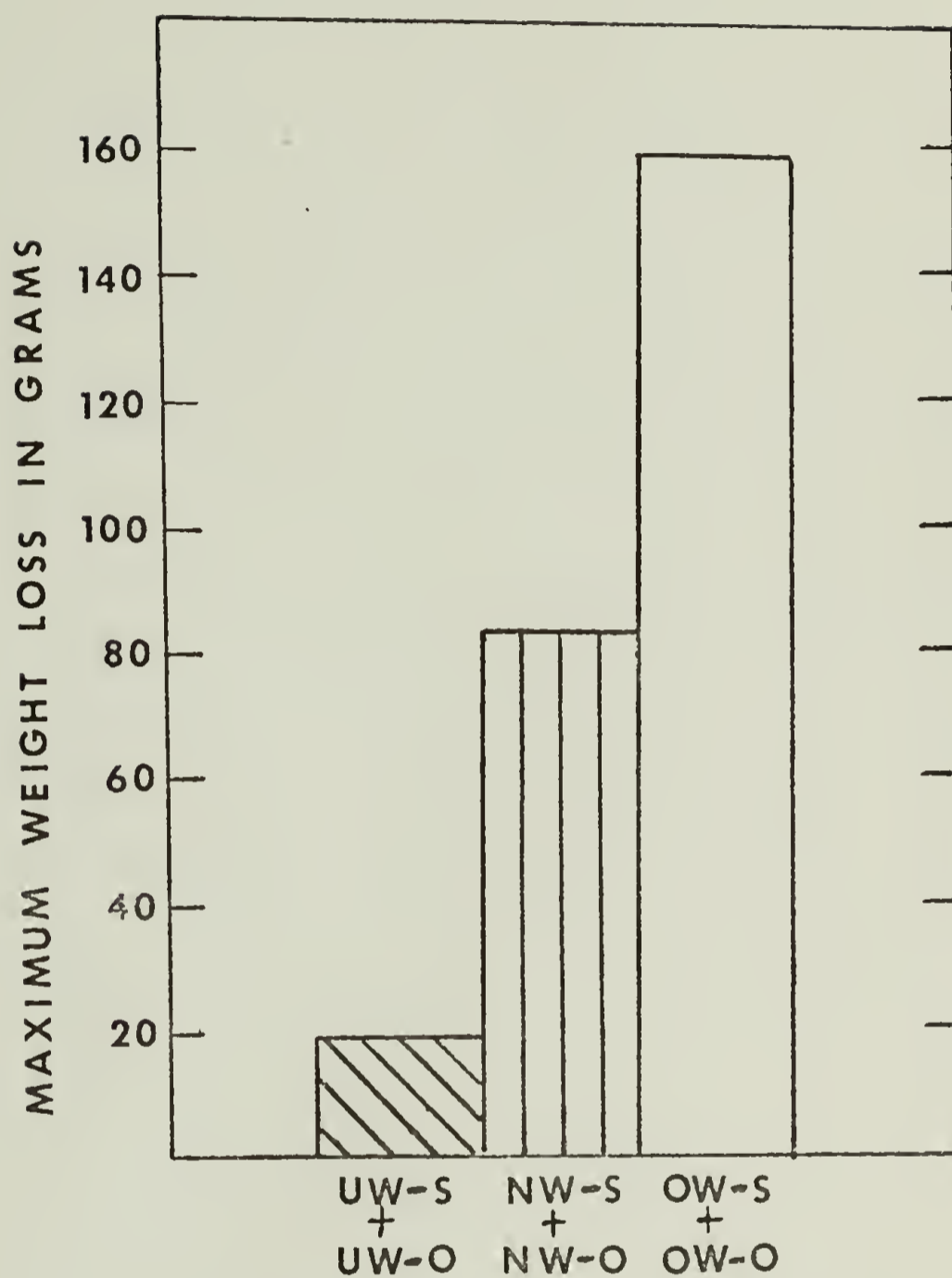


Figure 3. Represents the maximum weight loss following lateral hypothalamic lesions. Since there were no significant differences between the ovariectomized and the sham groups across each weight category their data were combined.

Figure 4. Mean daily food intake following lateral hypothalamic lesions.

FOOD INTAKE IN GRAMS

0 5 10 15 20 25 30 35

1 10 20 30

DAYS

- UW-S
- NW-S
- OW-S
- UW-O
- NW-O
- OW-O
- ▲
- 
- 
- 
- 

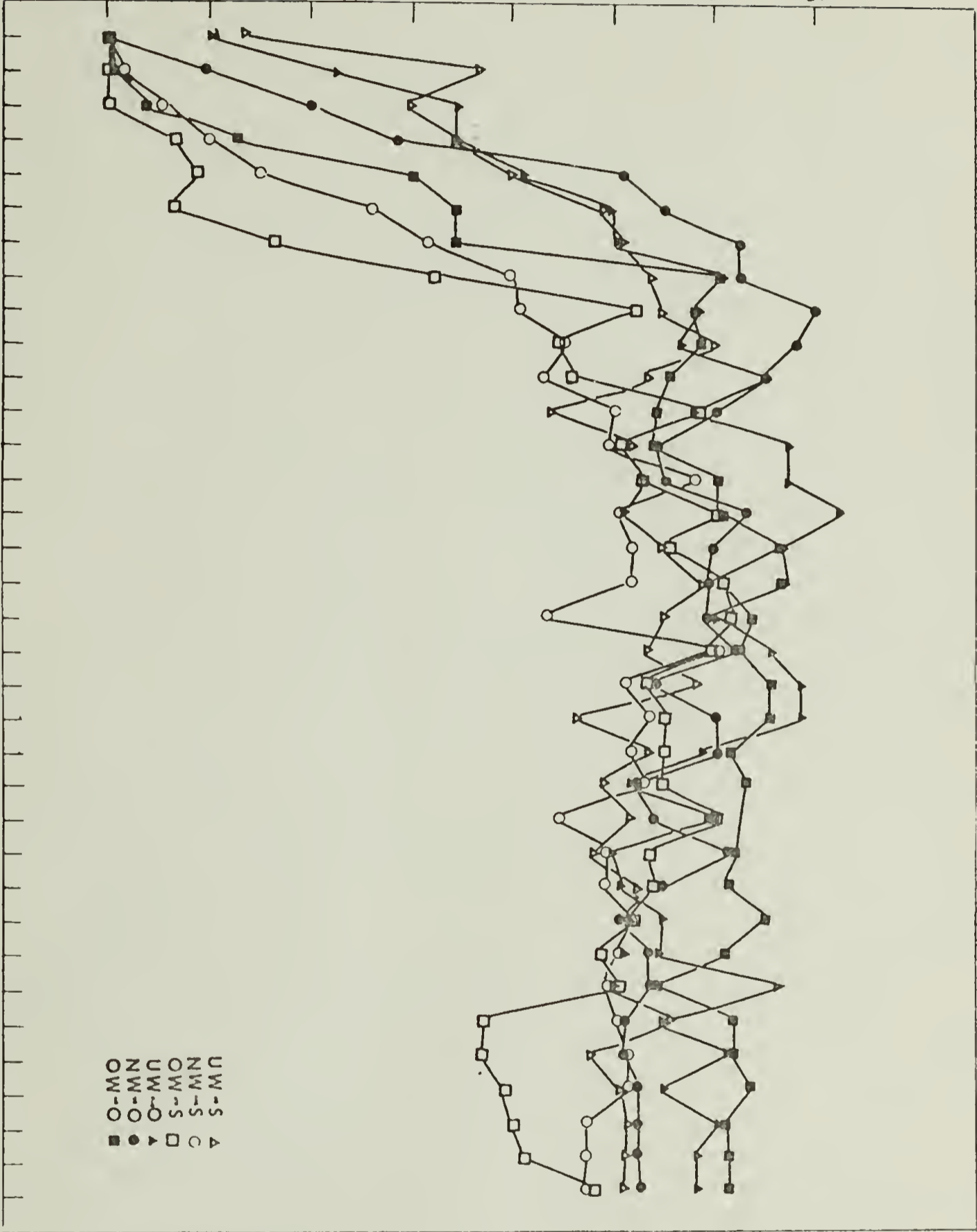
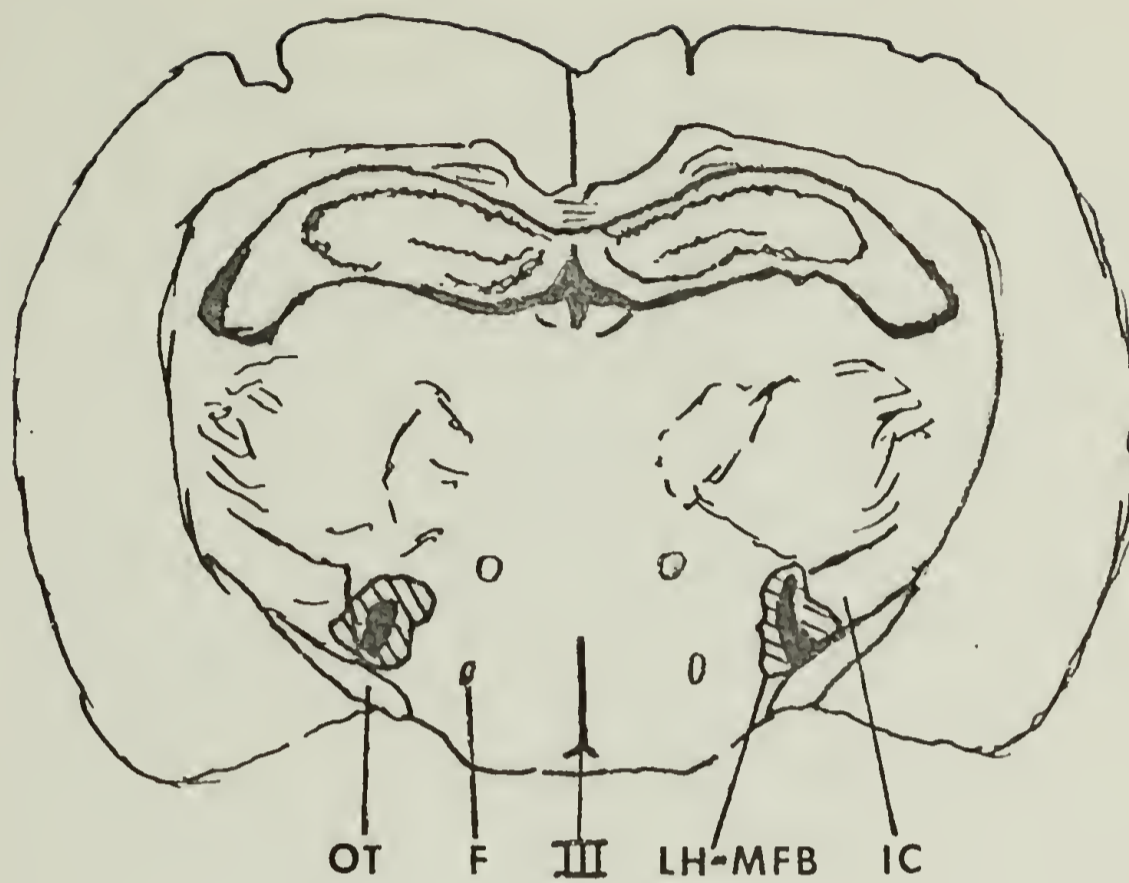


Figure 5. Diagrammatic representation of the brain lesions in the sham and ovariectomized groups. The striped area represents the largest lesion, while the dark area represents the smallest. (F= fornix, I.C.= internal capsule, LH-MFB= lateral hypothalamic-medial forebrain bundle area, O.T.= optic tract, III= 3rd ventricle).

SHAM



OVARIECTOMIZED

