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SOME BEHAVIORAL AND METABOLIC EFFECTS OF LATERAL HYPOTHALAMIC LESIONS

KENNETH PAUL VON DER PORTEN

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SOME BEHAVIORAL AND METABOLIC EFFECTS OF LATERAL
HYPOTHALAMIC LESIONS

by

KENNETH P. VON DER PORTEN

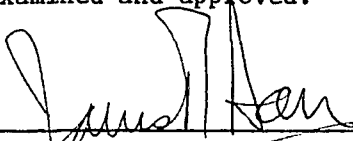
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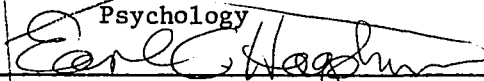
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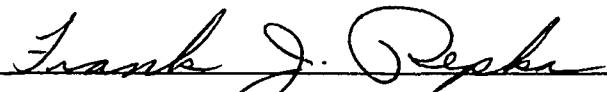
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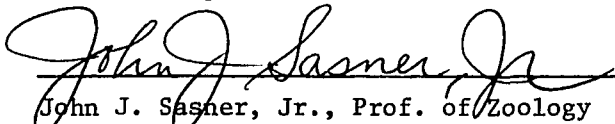
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ABSTRACT

SOME BEHAVIORAL AND METABOLIC EFFECTS
OF LATERAL HYPOTHALAMIC LESIONS

by
KENNETH P. VON DER PORTEN

This experiment investigated the effects of lateral hypothalamic lesions on metabolic rate and gross locomotor activity. Lesions in the perifornical lateral hypothalamus resulted in animals that displayed symptoms of Teitelbaum and Epstein's (1962) lateral hypothalamic syndrome. Recovery from the lesions appeared to occur in four stages. Early during recovery the animals appeared to be affected by the palatability of the diet that was offered. The lateral hypothalamic lesioned rats were hypodipsic, but did not appear to have any impairment in salivary control. These lesions did not produce any impairment in metabolic rate. Both laterally lesioned and control animals had a small (6.5%), but statistically significant rise in post operative metabolic rate.

This study did demonstrate that the chronic reduction in spontaneous locomotor activity that has been reported for lateral hypothalamic lesioned rats (Gladfelter & Brobeck, 1962; Gladfelter, 1971) is not a necessary consequence of these lesions. Only one animal showed a clear decrease (-27%) in spontaneous wheel running. Four other animals had small decreases and two animals increased their running slightly following lateral hypothalamic lesions. The changes in wheel running were not correlated with severity of feeding or weight regulation deficits.

These data support the position (e.g. Morgane, 1961a,b, 1975) that

the LH syndrome is not unitary nor invariant. Selective damage to different neural systems in the ventral diencephalon can produce distinct deficits that can be dissociated from one another. These deficits may or may not be related to the lesion-induced depletion of the neurotransmitters noradrenaline and dopamine. The technique of electrolytic lesions does not allow a precise method of evaluating this hypothesis however.

INTRODUCTION

Lateral Hypothalamic Syndrome

The lateral hypothalamic (LH) area has a long history of experimental investigation associated with it. These investigations have been concerned with various aspects of the homeostatic control of ingestive behavior. Anand and Brobeck (1951) originally described the starvation following lesions placed in this area of the rat diencephalon. They noted a prolonged aphagia due, they posited, to the destruction of a brain center primarily concerned with the motivation of feeding. Teitelbaum and Stellar (1954) discovered that if these completely aphagic and adipsic animals were tube fed, adequately hydrated, and carried over the acute starvation phase, a period of recovery could be demonstrated. Although the animals could eventually maintain their weights on a standard diet of dry rat chow and water, Teitelbaum and Epstein (1962) later determined that the recovery was not complete. These investigators described four invariant stages from the total aphagia and adipsia to the stage of apparent recovery.

Animals in the initial phase (stage I) refuse all food and do not drink any water. Without intubation, they will starve to death. This was the phenomenon that Anand and Brobeck described in 1951. Teitelbaum and Epstein (1962) noted further that food appeared to be actually aversive. If wet food was placed in their mouths, the LH lesioned animals actively wiped it away.

While the first stage is best described by the terms aphagia and adipsia, if carried past this variable time period, a stage of anorexia and adipsia occurs. Now the animals will eat wet and highly palatable foods (e.g. wet chocolate chip cookies) but will still refuse their normal diet of dry rat chow pellets and will not drink water. In this

second stage, feeding is still not adequate to sustain life and feeding by gavage must be continued.

The third stage is characterized by continued adipsia with a secondary dehydration aphagia. That is, since they still do not drink spontaneously, they will not eat their standard dry rat chow diet. They can now regulate their weights on wet and palatable foods but they still refuse water. If adequately hydrated by chronic intragastric intubation they will feed normally however.

Stage four has been termed recovery since the animals will now drink tap water and eat dry pellets. More sensitive tests reveal persistent abnormalities in their ingestion patterns however. These irregularities center primarily on chronic body weight and the inability to regulate water intake. Some of these "recovered laterals" will not respond to dehydration from intraperitoneal hypertonic saline injections. If they are required to take their daily water during a two hour period during the day, they fail to drink enough, as normal animals will, to maintain their weights. It was found that these recovered animals were prandial drinkers, i.e. they drink only when they eat.

Other tests of regulatory control have been performed on recovered lateral animals. Stricker and Zigmond (1976) have recently summarized some of these additional residual deficits reported in the literature. These have included 1) loss of feeding in response to glucoprivation (Epstein and Teitelbaum, 1967; Epstein, Nicolaidis and Miselis, 1975). When injected with either insulin or 2-deoxy-d-glucose, recovered laterals will not increase their food intake as normal animals will. 2) Impaired control of salivary reflex, leading to inefficient feeding (Kisseleff and Epstein, 1969) and loss of thermoregulatory grooming in the heat (Stricker and Hainesworth, 1970) is seen. 3) Also occurring is

the loss of specific hunger for sodium usually seen during sodium deficiency (Wolf & Quartermain, 1967) and poor learning to avoid a distinctly flavored solution associated with a poison (Roth, Schwartz & Teitelbaum, 1973). 4) A chronic reduction in metabolic rate (Davis, 1977) has been reported as well.

5) Finally, Powley & Keese (1970) noted that their recovered laterals maintain their body weights at a constant percentage below normal controls'. The decline to the new weight plateau appeared quite orderly and suggested to them that the animals were actively limiting intake in order to regulate their weights at the new lowered set-point. They observed further, that if their animals were pre-starved prior to surgery, a period of hyperphagia could be demonstrated. The animals now were presumably responding to a too low body weight by increasing intake. Because the regulation that was seen with these animals appeared to parallel the long term control of stable body weight in the intact adult organism, they hypothesized that the LH is directly involved in the maintenance of a stable weight set-point.

Motivational Deficit

A number of explanations have been proposed to account for the collection of fairly consistent symptoms seen in the LH syndrome. Most attention has focused on the original proposal that there is a primary motivational deficit underlying the aphagia and adipsia (Anand & Brobeck, 1951; Teitelbaum & Epstein, 1962; Rodgers, Epstein & Teitelbaum, 1965). Three kinds of evidence are usually presented in support of this position. First are the effects of electrical and chemical stimulation of the LH. Electrical stimulation can elicit eating or drinking (Greer, 1955; Mogenson & Stevenson, 1966; Valenstein, Kakolewski and Cox, 1969). If putative neurotransmitters are applied to the LH via indwelling

cannulae, eating (Slangen & Miller, 1969; Leibowitz, 1974) or drinking (Fisher & Courey, 1964) can be elicited as well. In many respects these behaviors resemble normally motivated responses to hunger and thirst. Second is the apparent active aversion for food in the early stages of recovery, and third, the overriding importance of palatability in controlling feeding in LH lesioned animals (e.g. Rodgers et al., 1965).

Partially as a result of these data, and from other studies as well, the hypothalamus has been viewed for a long time as the major brain center involved in motivated behavior (e.g. Stellar, 1954; Mogenson & Phillips, 1976). Conceptualizing damage to the LH by electrolytic lesions as destroying part of a primary motivational system is completely consistent with this long standing opinion. Furthermore, recovery of function after brain damage has been demonstrated for other neurally mediated behaviors. The basic premise of this theory is that the neural tissue damaged by these lesions is directly responsible for the motivation of ingestive behavior. During the variable time period after destruction of a variable amount of this tissue, the organism experiences a primary motivational deficit for food and water. The gradual recovery of function that is seen is due to the ability of the non-damaged tissue surrounding the lesion to gradually take over the functions of the damaged tissue. Thus, Teitelbaum and Epstein (1962) found a reinstatement of the syndrome when recovered (stage IV) lateral animals were re-lesioned. These animals had more severe and persistent symptoms after the second lesions were made.

Motor Deficit

Baillie and Morrison (1963) and Morrison (1968) questioned the motivational deficit interpretation of the LH syndrome. They believe that true aphagia should be distinguished from anorexia. In the former,

the animal cannot perform or coordinate the motor acts that constitute normal feeding. Anorexia describes the lack of motivation to eat.

These investigators believe that the LH syndrome involves a true (i.e. motor) aphagia rather than anorexia. The evidence in support of this interpretation is as follows. LH lesioned animals that refuse food will press a lever in order to deliver liquid food intragastrically (Baillie & Morrison, 1963). Lesions in the far lateral LH, which Anand and Brobeck (1951) described as most effective in producing aphagia, interrupt efferents from the internal segment of the globus pallidus, a structure with known motor functions in the rat (Rodgers et al., 1965). Also, Morgane (1961a), has shown that damage to the globus pallidus, or directly to its efferent pathway, can produce a severe aphagia.

Motor dysfunction has been described in a variety of forms with destruction of subcortical areas. Lesions of the basal ganglia and striatum have very diverse extra-pyramidal effects in mammals. Destruction of tissue in the posterior hypothalamus results in somnolence in a number of species (Nauta, 1946; Ransom & Ingram, 1932). It is generally believed however, that this effect is due to destruction of neural elements that are distinctly posterior to the most potent LH syndrome locus (i.e. at the rostro-caudal level of the ventromedial nucleus). Teitelbaum and Epstein (1962), in their original description of LH animals stated that the physical appearance of aphagic rats in the early stages of recovery as being hunched and inactive (p. 75).

Various other forms of motor abnormalities have been reported. Gladfelter and Brobeck (1962) and Gladfelter (1971) found that large hypothalamic lesions could virtually eliminate all spontaneous wheel running in food deprived rats. This large decrease in running was seen in animals that were aphagic, and in those that were not. These

investigators were not attempting to determine the nature of the relationship between activity and aphagia, and their lesions were placed diffusely throughout the ventral diencephalon. It is difficult, therefore, to draw any conclusions from either Gladfelter and Brobeck's (1962) or Gladfelter's (1971) data about motor impairment and the LH syndrome.

Morrison (1968) reported abnormal spontaneous stabilimeter activity in LH lesioned animals that seemed to coincide with the duration and severity of the feeding deficits that were produced by the lesions. He found an increase in rate of oxygen consumption and stabilimeter activity after lesions were placed that resulted in persistent aphagia. That is, the oxygen consumption and activity changes were permanent when the aphagia was permanent. Morrison's (1968) animals were only studied for a ten day period after lesioning, while Gladfelter and Brobeck (1962) and Gladfelter (1971) studied activity changes over a period of months. It is also possible that conflicting results can be obtained depending on how activity is measured, i.e. spontaneous wheel running vs. stabilimeter activity (Campbell, 1964). It should be noted that the sensitivity of Morrison's (1968) apparatus was such that he even recorded breathing movements, a behavior not normally included in measures of stabilimeter activity.

Finally, Balagura, Wilcox and Coscina (1969) investigated ventral diencephalic lesions and activity and found both aphagia and hypokinesia. Their conclusion was, however, that these two effects could be independent of one another. Motor dysfunction did not appear to be consistently related to aphagia. Using four behavioral measures of hypokinesia they found near zero rank order correlation coefficients between severity of aphagia and their index of motor impairment. Their data, like Morrison's (1968) was based only on the few days after lesioning when aphagia was

present, and did not include either stabilimeter or running wheel measures.

Neuroanatomical and Neurochemical Diversity of the LH

It is generally recognized that the LH is neurally quite heterogeneous, containing both ascending and descending sensory and motor components (Wayner, 1975). Raisman (1970) has observed that the well defined nuclei of the hypothalamus lie in the medial region, while most of the fiber systems occur in the LH, where cell bodies are scattered diffusely through the ascending and descending fascicles. The motor vs. motivational deficit issue therefore probably represents an oversimplification. Morgane (1961a,b, 1975) has argued against the existence of a unitary LH "syndrome." He has written that in over two hundred rats, small, selective lesions in the LH, globus pallidus, subthalamus and pallidal efferent pathway produced numerous distinct variations on the LH theme. He reports nothing resembling an invariant constellation of events or recovery processes. The type and degree of symptomatology varied clearly with the extent and anatomical locus of the lesion. He has argued that anatomically, the LH doesn't resemble a "center" (i.e. it is not a discrete nuclear mass) whose destruction would result in a unitary syndrome. Raisman (1970) has written that it is still largely a matter of speculation as to what extent the LH area may contain discrete functional and anatomical systems. Morgane (1975) believes that such a behaviorally complex response as feeding should not be controlled by any single brain region. He observed that part of the problem may be that only aphagia and adipsia are measured because of the preconceptions of the investigators, and the obvious, drastic consequences these deficits have for the organism. The question then becomes whether the feeding and drinking disturbances are primary or secondary effects

of the lesions.

In 1961a Morgane attempted to differentiate a far lateral from a midlateral LH effect. While both lesions impaired feeding, the far lateral included a metabolic anomaly as well. Regression curves of body weight on days for his animals showed that they lost weight significantly faster than did normal controls deprived of food and water. Because of the involvement of the globus pallidus, Morgane (1961a) concluded that this structure is involved in motor aspects of feeding and drinking, and that it exerted some undefined metabolic effects related to energy homeostasis.

Stevenson and Montemurro (1963) reported results similar to Morgane's. Although the histology was not reported, their LH lesioned animals were aphagic and also had elevated rates of oxygen consumption within 24h of lesioning. There followed a steady decline until at 72h post operatively, their metabolic rates were back to normal. The most important effects of these lesions then may be a disruption of fiber tracts passing through the LH which control important neural regulatory (e.g. neuroendocrine) mechanisms. Disruption of feeding and accompanying weight decrements have been associated with disruption of two of the major fiber tracts in the LH.

The medial LH (perifornical area, medial forebrain bundle: MFB) is almost exclusively noradrenergic (NA) with a small proportion of serotonergic (5-HT) fibers. The ascending NA system contains a dorsal segment arising from cell group A6 in the locus coeruleus which primarily innervates the meso- and neocortex. More importantly, the ventral ascending NA fibers innervate the LH, basal forebrain structures, and parts of the limbic system. This latter system arises from cell groups A1, A2, A5 and A7 in the midbrain reticular formation (Fuxe, Hökfelt & Jonsson, 1970).

These investigators believe that this ventral pathway has important neuroendocrine control functions.

The far lateral LH (medial internal capsule), while anatomically contiguous with the MFB, contains a large population of dopaminergic (DA) fibers. The somata of these fibers lie in the midbrain, anterior to the cell bodies of the NA system. Cell groups A8 and A9 are in the substantia nigra, and their axons form the nigro-striatal bundle (NSB), which contains about 75% of the total brain DA (Iversen & Iversen, 1975). The NSB projects together with the NA fibers in the MFB through the LH, with the NSB lying more laterally than the main MFB. The DA fibers of the NSB leave the MFB more posteriorly to innervate the corpus striatum (caudate nucleus & putamen) and globus pallidus. The far lateral lesions therefore tend to impinge upon the NSB as well as the MFB. Lesions resulting in aphagia and weight loss have been reported in both the medial LH (Morgane, 1961a; Oltmans & Harvey, 1972, 1976; Davis, 1977), and the far lateral LH (Morgane, 1961a; Oltmans & Harvey, 1972, 1976).

Possible Neuroendocrine Involvement in the LH Syndrome

In 1955 Harris postulated that the anterior pituitary and hypothalamus interacted via a neurovascular link. While the posterior lobe was known to have direct neural input from the supraoptic and paraventricular nuclei, it was known that the anterior lobe was not so directly connected with the ventral diencephalon. Much research has involved elucidating the possible mode of neuro-vascular communication between the CNS and adeno-hypophysis. Halász's description of the deafferentation technique (1972) demonstrated that tonic endocrine function could continue when an area of the ventro-basal hypothalamus was completely separated from the surrounding neural tissue. Halász, and many others since have demonstrated that the hypothalamus controls the release of

trophic hormones from the anterior pituitary by peptide "release factors" (RFs) that are transported to the adenohypophysis by the portal blood supply around the median eminence. Halász (1972) found that the area involved in the release (and presumably synthesis and storage) of these factors in the rat brain to be 0.50-1.0mm lateral to the midline, and including the suprachiasmatic, paraventricular, periventricular, anterior hypothalamic, arcuate, premammillary, and the medial halves of the ventromedial nuclei. This critical mediobasal site has been termed the hypophysiotrophic area (HTA) by Halász.

While it was demonstrated that an isolated hypothalamic "island" containing the HTA could maintain tonic basal output of the anterior pituitary, it was evident that a second, higher level control existed, and comprised extra-HTA structures. Thyrotrophin release factor (TRF) was chronically reduced, and sex hormones involved in the female rat's estrous cycle failed to show the normal periodicity in animals sustaining these hypothalamic islands. Halász (1972) speculated that this second control level receives and integrates environmental as well as internal neural stimuli influencing anterior pituitary function. In addition, it appears that the elements at this second, higher order control level are catecholaminergic (CA; Ganong, 1972, 1974; Annunziato, Di Renzo, Lombardi, Scopacasa, Schettini, Preziosi & Scapagnini, 1977). Evidence has been provided by both Ganong (1972, 1974) and Annunziato et al. (1977) that TRF release appears to be stimulated by ascending NA fibers, and that the receptors appear to be alpha adrenergic. These later investigators found, for example, that the acute release of thyroid stimulating hormone (TSH) in response to cold was blocked by pre-treatment with the tyrosine hydroxylase inhibitor alpha-methyl-para-tyrosine. This block could then be reversed by the administration of a

central NA stimulant (clonidine). The evidence for the noradrenergic nature of TRF-TSH release, and its alpha adrenergic nature fits well with the previously cited work on chemical stimulation of the LH and eating (Slangen & Miller, 1969; Leibowitz, 1974). These investigators demonstrated an increase in feeding when NA was injected into the LH. Leibowitz (1974) found that an alpha adrenergic blocker (phentolamine) could block the effect, indicating the alpha adrenergic nature of the response. It seems possible, therefore that the mechanism underlying NA induced eating might be related to the control of TRF-TSH release. Increased metabolic rate would be the final step in response to the exogenously applied NA, with increased feeding in response to the higher metabolic rate as the ultimate outcome. The time course for NA induced eating is completely compatible with this proposed mechanism (Davis, 1977).

If the chronic reduction in body weight that is a persistent symptom of LH lesions is considered, one explanation that is immediately suggested is that these lesions disrupt a primary source of excitatory afferent input to the HTA. This explanation has recently been suggested by Davis (1977) and is much more compatible with the known anatomical structure of the LH (cf Raisman, 1970; Morgane, 1975). If just a disruption of the hypothalamic-hypophyseal-thyroid axis is considered, the reduction in body weight could be seen not as a primary motivational or motor deficit, but rather as a secondary consequence of a reduction in circulating thyroxine (T_4). Although a number of hormones could be affected by these lesions, TSH is probably the best single candidate. Mess, Zanisi, and Tima (1970) noted that of all the release factors, TRF has the most extended representation in the HTA, being diffusely produced in this entire area. It is also agreed (Mess et al. 1970) that

besides the HTA, TRF is also present in the entire hypothalamus. The exact role of the extra-HTA TRF is unclear, but it might be involved in the feedback control of NA synthesis, since Stolk and Nisula (1975) have reported that there is evidence that TRF regulates the biosynthesis of NA in some brain sites.

The possibility of a metabolic imbalance in the LH syndrome has already been suggested. Both Morgane (1961a,b) and Stevenson and Montemurro's (1963) data indicated short term increases in metabolic rates for their rats. It was proposed by the later investigators that the resultant weight loss was due in part to the hyper-metabolism, coupled with some degree of (motor?) aphagia; or at least to an inability to compensate for the hypermetabolic state by increased feeding. Davis (1977) showed however, that the long term effects of these lesions might be a hypometabolic condition. In one study, LH lesioned rats that had lost at least 15% of their prelesion body weight had significantly lower fasting heat productions (FHP; metabolic rate in 17h deprived, unrestrained animals) than control animals maintained at a reduced body weight which was comparable to the lesioned animals'. While it is not clear how a hypometabolic state could account for the initial, dramatic period of aphagia and adipsia, the chronic reduction in body weight (e.g. Powley & Keeseey, 1970) could be explained by the lesion induced hypothyroidism. Since the amount and effectiveness of growth hormone (GH) diminishes with decreases in blood thyroxine (Wilkins, Mayer and Vanderlaan, 1974), the reduction in postlesion growth may be related to GH deficiency. This argument would be especially relevant to animals lesioned early during their growth. Davis (unpublished) has found a high correlation between final postlesion weight and rate of preoperative growth.

These ascending NA fibers might also be involved in monitoring

and/or controlling the rate of synthesis, storage or release of TRF from the hypophysiotrophic area in response to the organism's varying energy requirements. Considering the evidence that recovered lateral animals often lack glucoprivic control, it may be that the LH is involved in the detection and control of energy utilization (i.e. rate of glucose utilization, Epstein et al. 1975). This parameter would be expected to be intimately related to metabolic rate and ingestive behavior. The LH has often been suggested as being part of a central "glucostat" (Mayer, 1955), responding to changes in glucose utilization with changes in hunger leading to feeding and satiation. Some have argued against such a mechanism (Russek, 1975) or questioned the necessity of postulating a central glucostat at all. The account of the LH as part of Halász's second level of control, at least for TRF, might then be a mechanism by which an organism does respond to energy balance changes by feeding.

Metabolic Rate, Locomotor Activity and the LH Syndrome

A major problem in describing the nature of the metabolic changes occurring with LH lesions is the involvement of changes in locomotor activity. This problem is two-fold. First, there is the large effect of locomotor activity on metabolic rate. This is the well known fact (e.g. Knoebel, 1966) that the more active an animal is, the higher the metabolic rate. Typically, metabolic rate is measured for an unrestrained, freely behaving subject. Second is the previously cited evidence for disruption of normal locomotor activity due to LH lesions (Gladfelter & Brobeck, 1962; Gladfelter, 1971; Morrison, 1968; Balagura et al. 1969). It is extremely important then to include activity measures when LH lesions and metabolic rate are under investigation. Morrison (1968) came closest to doing this, however his data is difficult to relate to the LH syndrome. He used only a highly palatable liquid diet postoperatively

and it is impossible to differentiate the time course of any aphagia or adipsia that his animals might have suffered. Furthermore, he measured only stabilimeter activity over a short (10 day) period, and the size of the lesions he used (1.5ma for 10-20 sec) precluded any useful anatomical data.

Whether metabolic changes can occur independently of activity changes is unknown. It is not even clear what the nature of the locomotor changes are. As noted previously, conflicting results have been reported. These results could possibly be due to the differences in lesion sites (e.g. medial LH vs. far lateral LH) or to the measure of activity employed (e.g. running wheel vs. stabilimeter vs. rating scales of activity). It is even possible that some of the metabolic abnormalities that have been reported are due to activity level changes of the animals. Thus, the lowered FHPs of Davis' (1977) animals may have been due to lesion induced hypoactivity (Gladfelter & Brobeck, 1962; Balagura et al. 1969).

This study is therefore an attempt to relate LH lesions that result in chronic weight loss to possible metabolic abnormalities and changes in activity. Because of the different results that can be obtained by using different measures of activity (cf Campbell, 1964), both running wheel and stabilimeter measures were taken. In the latter case, this was done while the animals were having their metabolic rates measured.

METHOD

Animals

Male CD-Fisher inbred albino rats were obtained at approximately 200g from the Charles River Breeding Labs. All animals were initially maintained in a vivarium with a 12 hour light/dark cycle until they were approximately 250-300g. At about this time they began the initial phase of baseline testing. All animals were fed Purina rat chow pellets.

Prelesion measures

Activity Wheel Baseline. Six animals at a time were housed in standard activity cages (Wahmann Manufacturing Co., model LC-34). Each combination home cage and fourteen inch diameter running wheel was enclosed in an individual light proof, sound attenuated wooden cabinet (inside dimensions: 61x47x40.5 cm). Each cabinet had a fan that forced fresh air in through a light baffle. An exhaust port and light baffle were also provided, and the temperature inside the cabinet was between 20° and 23° C.

The diurnal illumination within each cabinet was remotely programmed for six hours of light (7½ W light bulb, on at 0900) and eight hours of darkness (starting at 1500). At the beginning of every other six hour light period, the cabinets were opened and the animals were weighed and their food and water replenished. During the entire remaining time they were isolated from all external stimuli and allowed to run ad-lib in the wheels. The total number of revolutions run during each light and each dark period was recorded on remote counters, outside of the cabinets.

A fourteen day period was found to be sufficient for running to stabilize under these conditions. A measure of each wheel's rolling resistance (frictional torque, Lacey, 1944) was recorded at this time

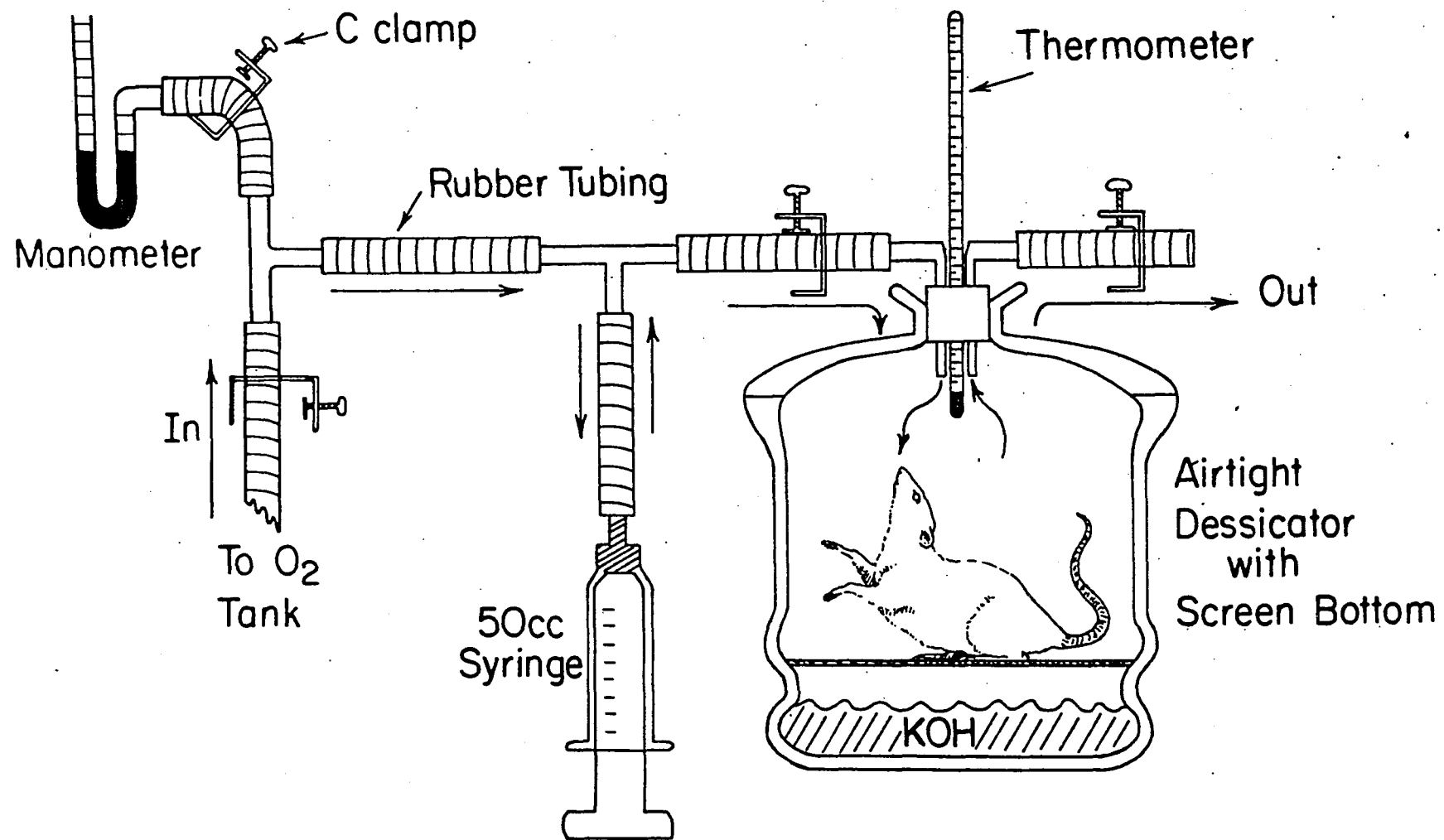
as well.

Food & Water Intake. Following baseline wheel running determinations, all animals were housed in individual cages in a vivarium with the same diurnal light/dark cycle as the activity wheels. The ambient temperature in this room was $25 \pm 2^{\circ}$ C. Five days of total 24h food and water intake measures were taken. Food consumption was measured by weighing the remains of a premeasured amount of food that was given to the animal on the preceding day. All crumbs were collected under the cages on newspaper and included in the weighing. Water consumption was measured by weighing the animals' water bottles. A water bottle placed on an empty cage was also weighed to estimate spillage, and all water measures were corrected for the amount of water loss due to removing and replacing the bottles.

Metabolic Rate & Stabilimeter Measures. Each animal had its fasting metabolic rate measured by a technique similar to the one originally described by Benedict and McLeod (1929, fig. 1). While deprived of food and water for seventeen hours, the animal was placed in the glass dessicator (155mm diameter, 100mm high) containing KOH, which was then flushed with oxygen for at least five minutes. The temperature inside the dessicator was between 23 and 24° C. Because of the constant temperature of the dessicator and its small size, measurements were not corrected to standard temperature and pressure of dry gas conditions.

The time required to consume one syringe (50cc) of O_2 was then measured with a stop watch. About six such determinations were made for each animal per trial (about one hour duration). A total of three such prelesion trials were run for each animal. The use of two syringes and two-way stopcocks allowed the six determinations to be made continuously over the approximately hour long trial.

Figure 1: Schematic diagram of the closed loop calorimeter. The tubing and control valves in the present experiment were doubled to allow continuous flow of oxygen between trials.



The dessicator rested on a spring mounted pan which served as part of the stabilimeter. Movements of the animal within the dessicator were recorded by a crystal pickup and amplifier circuit (e.g. Thiel, Barnes & Mrosovsky, 1972; Brakel, Babb, & Mahnke, 1971; Springer & Miller, 1973). After being amplified, this signal triggered a one-shot if the voltage exceeded the value set by the voltage comparator circuitry. The sensitivity was set so that a 7.85g weight dropped from a height of 4cm would record one count. The output of the one-shot was then recorded on an electronic counter. Activity counts were recorded for each 50cc metabolic rate determination (approximately ten minutes long), and the mean of the six activity determinations calculated. The animal's activity during each 50cc determination was also rated by the experimenter on a scale of 0 (no activity or asleep) to 4 (extremely active).

Because the stabilimeter means were highly correlated with their respective standard deviations, a square root transformation: $\bar{X}' = (\bar{X} + 0.50)^{0.50}$ was applied to the stabilimeter means. Because some of the means were less than 10, 0.50 was added to all the means (Kirk, 1968). The interdependence of the means and standard deviations was successfully removed by this transformation, and all analyses of activity data are based on these transformed means (\bar{X}').

The time required to consume 50cc of O_2 was converted to the rate measure: $\text{ml } O_2/\text{min}/\text{kg}^{.75}$.

Surgery

The animals were divided into a LH lesion group (n=8) and a sham control group (n=6). Bilateral lesions were made using anodal direct current (1 ma for 15 sec) with a rectal cathode from a Stoelting lesioning device. The anodal electrode was a 00 gauge stainless steel insect pin insulated with EpoxyLite. The tip was ground flat until the exposed cross-section had a diameter of 0.2mm.

The external coordinates for the lesions were 3.00mm posterior to bregma; 1.5mm lateral to the saggital suture; and 8.3mm below the dorsal surface of the skull with lambda and bregma in the same horizontal plane. These coordinates placed the lesions in the LH at about the rostro-caudal level of plate 32 in the rat brain atlas of König & Klippel (1963). Two of the sham animals had the electrode positioned according to these coordinates, but no current was passed. The other control animals were inadvertently shams as a result of a malfunction of the lesion maker. They exhibited no LH syndrome symptoms and returned to normal weight immediately after surgery.

All surgery was performed under general (i.p. 45mg/kg sodium pentobarbital: Nembutal) and local (topical tetracaine HCl: Pontocaine) anesthesia. All animals were deprived of food and water for at least four hours prior to surgery.

Postlesion Measures

Food & Water Intake. Within one day of surgery, all animals had a measured amount of food and water presented to them, and daily food and water measures were begun as described previously.

If an animal did not eat, the dry lab chow pellets were replaced with ground chow mixed with water (1:1 by weight). If the animal still refused to eat and lost weight the next day, a similar mash was made of chocolate chip cookies and water (1:1 by weight). This last enticement was always sufficient to induce the animal to eat and regain some weight. The animal was then returned to the rat chow mash. If he still continued to eat, he was returned to the standard diet of lab chow pellets and water from a bottle. This last condition defined recovery from the LH syndrome, or "stage IV" (Teitelbaum & Epstein, 1962). The intake measures were continued for at least five days past the first day of recovery.

At least one month later, measures of degree of desalivation and hypodipsia were taken. The technique used was modified from that of Teitelbaum and Epstein (1962). The degree of desalivation was assessed by measuring the amount of food eaten in the absence of water for a 24h period. Hypodipsia was assessed by measuring the amount of water drunk in the absence of food during a 24h period. Two such determinations were made for each animal with at least three days of ad lib food and water between tests.

Activity Wheel Testing. Approximately 3-4 weeks after surgery, each animal was reintroduced to the same activity wheel that he had run in during the baseline determinations. Each wheel was tested to be sure that the frictional torque was the same as during the baseline conditions. All conditions during testing were identical to those in effect during baseline, including the alternate day maintenance schedule.

Metabolic Rate & Stabilimeter Measures. Three more, postlesion replications of the metabolic rate and stabilimeter data were obtained. At least four weeks intervened between surgery and the first metabolic rate determinations. The procedure used was identical to the prelesion baseline determinations.

Histology

At the conclusion of the experiment, the animals were perfused with normal saline followed by 10% buffered formalin. Each brain was then removed and allowed to sit in formalin for at least 24h. The brains were then frozen, and cut in 50 micron thick sections. Every other section throughout the extent of the lesion was mounted on a glass slide. Cell bodies were stained with cresyl violet and fiber tracts with luxol blue.

RESULTS

Food and water measures

When compared to the controls, the LH animals sustained weight decrements and feeding deficits postoperatively. Table 1 presents the animals' body weights at the time of surgery, and at the conclusion of the experiment. All but one of the control animals had gained weight slightly ($\bar{X} = 3.3\%$). All of the LH animals had lower body weights at the time they were killed ($\bar{X} = -13.5\%$). The animals were all essentially at their asymptotic weights at the time of surgery, and therefore percentage change from this time is a meaningful measure.

In terms of recovery from the effects of the lesions, most animals could be classified during recovery into Teitelbaum and Epstein's (1962) discrete stages. For example, animals that did not eat wet mash would eat and gain weight on a wet and palatable diet (chocolate chip cookie mash), if offered early during recovery. Because there was a relatively rapid progression through these stages, it was not possible to determine the exact duration of each. The time period from lesioning to complete recovery (ability to maintain weight on dry pellets and water) ranged from one day (CDF07, CDF37) to about eleven days (CDF13). A Spearman rank order correlation coefficient was computed for the time to recovery and percentage weight loss for the LH animals. The value of r_s was .857, indicating that animals that took longer to recover also sustained greater chronic weight reductions. These results are also included in table one. All control animals ate their normal diet and maintained their weight immediately after surgery.

The LH lesioned animals were hypodipsic as well (table 2). When compared to the controls, these animals drank, in the absence of any food, about half as much water as a group than the controls. Because of the

Table 1

Weight shifts and recovery data for LH and control animals.

		<u>weight at surgery</u>	<u>weight at sacrifice</u>	<u>% change*</u>	<u>days to recovery*</u>
Controls	CDF01	355	367	3.4	0
	CDF02	381	389	2.1	0
	CDF03	358	384	7.3	0
	CDF04	335	357	6.6	0
	CDF05	313	319	1.9	0
	CDF06	354	348	-1.7	0
		\bar{X} s	349 23.0	361 25.7	3.3
<u>LH</u>	CDF07	382	364	-4.7	1
	CDF09	405	346	-14.6	3
	CDF13	371	294	-20.8	11
	CDF14	353	283	-19.8	10
	CDF35	326	289	-11.0	7
	CDF36	330	294	-10.9	5
	CDF37	320	294	-8.1	1
	CDF40	297	244	-17.8	7
		\bar{X} s	348 36.1	301 37.5	-13.5 5.7

* $r_s = .857$ ($p < .02$; For LH animals)

Table 2

A. Mean water consumption (ml) in the absence of food; and mean food consumption (g) in the absence of water in 24h. B. Mean food (g) and water (ml) consumption during five day period after recovery. C. Mean baseline food (g) and water (ml) consumption.

	A		B		C	
	Food ¹	Water ²	Food	Water ³	Food	Water
CDF01	13.8	15.5	19.7	27.2	17.5	19.6
CDF02	16.8	1.5	23.6	29.6	18.8	25.8
CDF03	15.8	2.5	15.0	19.4	16.8	16.8
CDF04	14.8	3.5	15.9	21.8	17.3	18.6
CDF05	15.0	4.0	17.7	20.2	15.4	16.4
CDF06	16.4	24.0	22.6	30.2	20.8	20.2
\bar{X}	15.40	8.50	19.08	24.73	17.77	19.57
s	1.11	9.16	3.52	4.84	1.85	3.40
CDF07	16.2	1.5	17.5	20.3	17.1	16.6
CDF09	19.0	0.0	19.3	15.8	19.8	19.4
CDF13	18.4	0.5	13.8	13.8	18.9	22.0
CDF14	18.0	0.0	13.3	7.4	15.9	16.8
CDF35	19.4	8.0	15.3	15.7	20.0	20.0
CDF36	19.2	17.5	17.2	20.0	18.3	16.6
CDF37	19.2	3.0	20.3	17.0	16.8	17.2
CDF40	17.1	2.0	15.0	18.2	16.4	18.6
\bar{X}	18.30	4.06	16.46	16.02	17.90	18.40
s	1.15	6.02	2.53	4.13	1.57	1.96

¹ $\underline{t} = 4.71$ $p < .001$; LH vs. Controls

² $p = .071$ (Mann-Whitney U); LH vs. Controls

³ $\underline{t} = 3.63$ $p < .01$; LH vs Controls

non-normality of this data, a nonparametric test was used to determine the significance of the difference in the amount of water consumed between the two groups. The probability value associated with this difference was .071 (Mann-Whitney U), which just missed significance at the usual criterion level of .05. It is evident then that the groups formed in the present experiment might not be completely homogeneous with respect to LH syndrome symptomatology.

Surprisingly, the LH animals ate significantly more food in the absence of water than the controls ($\underline{t} = 4.71$, $p < .001$; table 2). When food consumption is compared for the first five days past recovery, the groups did not differ significantly, although the LH animals' mean food consumption was lower than the controls' (16.46g vs. 19.08g). The only other between group difference to reach statistical significance was that between the mean amount of water consumed during the five day period after recovery. The LH group drank 16.02ml, and the controls drank 24.73ml (table 2).

Metabolic Rate

The metabolic rate data appear in table three and figures two and three. An analysis of variance on rate of oxygen consumption ($\text{ml O}_2/\text{min}/\text{kg}^{.75}$) was performed (table 4). Lesion condition (LH vs. controls) was a between subjects variable, time (pre- and postlesion) and activity (basal and nonbasal) were within subjects variables.

As expected, there was a large and significant effect of activity on metabolic rate ($\underline{F}_{1,12} = 270.62$, $p < .001$). No significant difference was found for metabolic rate between the LH and control groups however. The only other significant factor was time ($\underline{F}_{1,12} = 10.30$, $p < .01$) with

Table 3

Individual Animal's Rate of Oxygen Consumption ($\text{ml O}_2 / \text{min} / \text{kg}^{.75}$) for all Three Conditions of the Experiment.

		<u>Prelesion</u>		<u>Postlesion</u>	
Basal	CDF01	10.17		10.00	
	CDF02	11.82		11.55	
	CDF03	10.30		10.31	
	CDF04	13.54	$\bar{X}=11.39$	12.98	$\bar{X}=11.61$
	CDF05	10.88	$s=1.25$	12.79	$s=1.24$
	CDF06	11.62	$s_{\bar{X}}=.51$	12.04	$s_{\bar{X}}=.51$
<u>Controls</u>					
Nonbasal	CDF01	13.38		14.55	
	CDF02	13.53		14.20	
	CDF03	12.53		13.08	
	CDF04	15.89	$\bar{X}=13.65$	15.94	$\bar{X}=14.52$
	CDF05	12.39	$s=1.28$	15.03	$s=0.95$
	CDF06	14.20	$s_{\bar{X}}=.52$	14.35	$s_{\bar{X}}=.39$
Basal	CDF07	10.18		12.66	
	CDF09	9.73		10.36	
	CDF13	12.50		14.04	
	CDF14	9.72		10.58	
	CDF35	12.88		14.18	
	CDF36	11.20	$\bar{X}=11.01$	11.07	$\bar{X}=12.19$
	CDF37	10.02	$s=1.28$	12.81	$s=1.48$
	CDF40	11.86	$s_{\bar{X}}=.45$	11.84	$s_{\bar{X}}=.52$
<u>LH</u>					
Nonbasal	CDF07	14.36		14.21	
	CDF09	14.45		13.19	
	CDF13	14.70		17.20	
	CDF14	11.96		14.50	
	CDF35	15.86		15.86	
	CDF36	15.40	$\bar{X}=14.31$	15.30	$\bar{X}=15.40$
	CDF37	13.87	$s=1.18$	16.40	$s=1.36$
	CDF40	13.88	$s_{\bar{X}}=.42$	16.55	$s_{\bar{X}}=.48$
		\bar{X}		\bar{X}	
		$\bar{X} = 12.60$		$\bar{X} = 13.48$	
		$s = 1.89$		$s = 2.02$	

Table 4

Analysis of Variance for rate of oxygen consumption ($\text{ml O}_2 / \text{min} / \text{kg}^{.75}$)

SOURCE	SS	df	MS	F
Between Groups		13		
Lesion (L)	2.61	1	2.61	.569
subjects/groups	55.00	12	4.58	
Within Groups		42		
Activity (A)	116.91	1	116.91	270.620***
A X L	1.55	1	1.55	3.58
A X subjects	5.18	12	.43	
Time (T)	9.67	1	9.67	10.30**
T X L	1.16	1	1.16	1.24
T X subjects	11.27	12	.94	
A X T	.31	1	.31	.60
A X T X L	.07	1	.07	.137
A X T X subjects	6.13	12	.51	

p<.001***

p<.01**

both the LH and control group having elevated rates of oxygen consumption after surgery. The lesion condition by time interaction (T X L) was not significant however, indicating that the increase across time was not different for the LH vs. control groups.

When the activity variable was dichotomized into basal (no stabilimeter counts; little or no observable movement) and nonbasal (everything else) values, the large and significant effect of activity is seen. When actual stabilimeter counts were correlated with metabolic rate, the coefficient of correlation was near zero. Due to the nature of recording activity in terms of discrete trials, and the continuous nature of metabolic rate, these two variables did not correlate highly when activity was expressed as a continuous variable. For example, an animal might be asleep for most of the trial, then wake up and register a large number of stabilimeter counts by grooming vigorously; while the metabolic rate, based on the length of the entire session, would be very low. The stabilimeter data, expressed as a continuous variable, will therefore be presented separately from the metabolic rate data (fig. 9).

Figures two and three are scattergrams for the regression of heat production (kcal/day) on body weight. The data points on which the regression was computed (closed circles, $n = 19$) represent all the animals in the study, prior to surgery, plus animals of the same strain, but with lower body weights. These younger animals were included to provide more variability in the predictor variable (weight) in order to more accurately describe the function relating body weight to metabolic rate. The LH animals' post lesion weights and metabolic rates are depicted on the scattergrams with the animals' number next to their respective data point. These values did not enter into the computation of the regression equation. It can be seen that the LH lesioned animals' data points

Figure 2: Scattergram of points for regression of basal heat production (kcal/day) on body weight (kg). Filled circles represent normal animals (n=19) on which regression equation was based. Open circles are LH animals' post lesion data. Dashed line represents standard error of estimate.

LOG KILOCALORIES / DAY

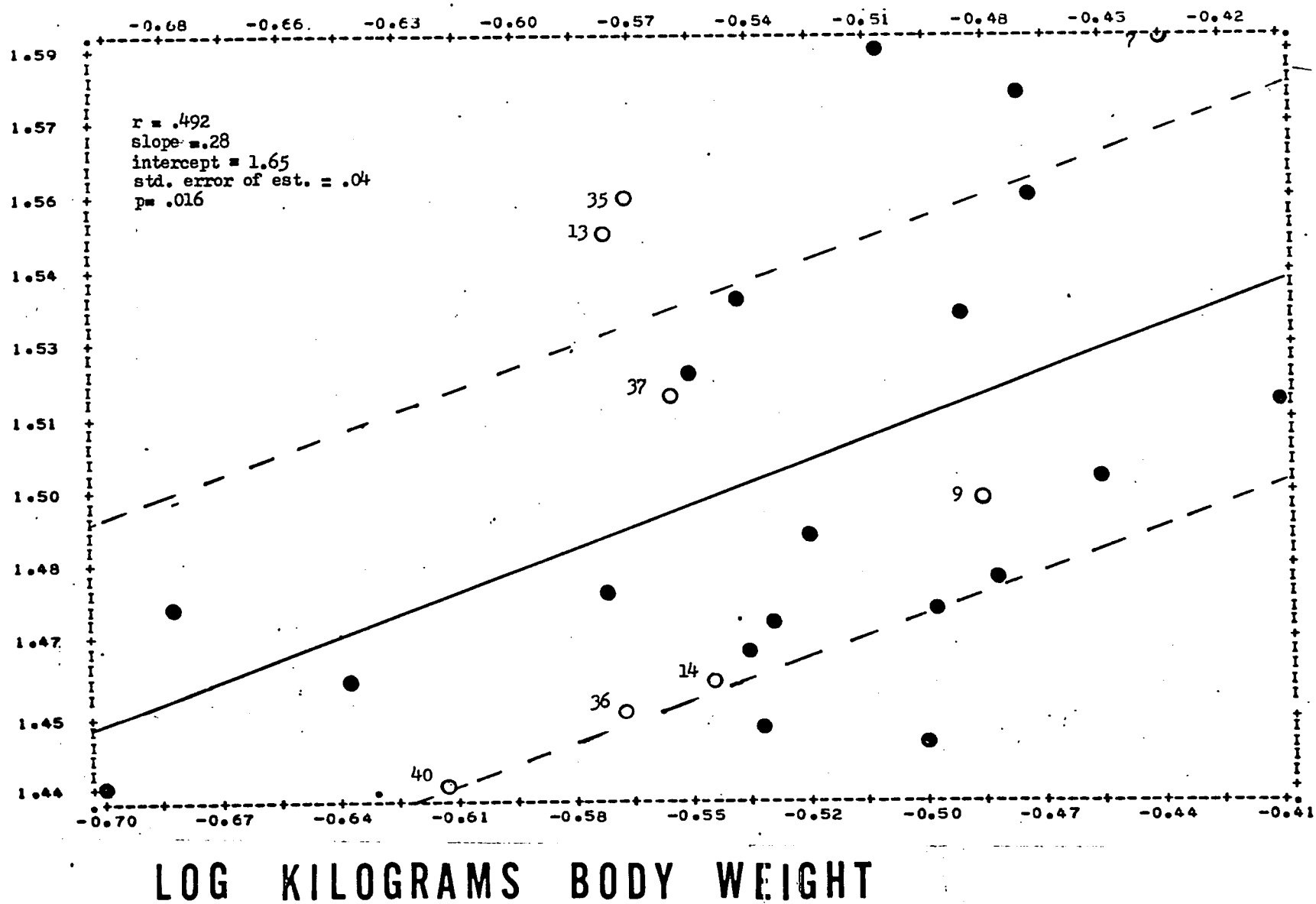
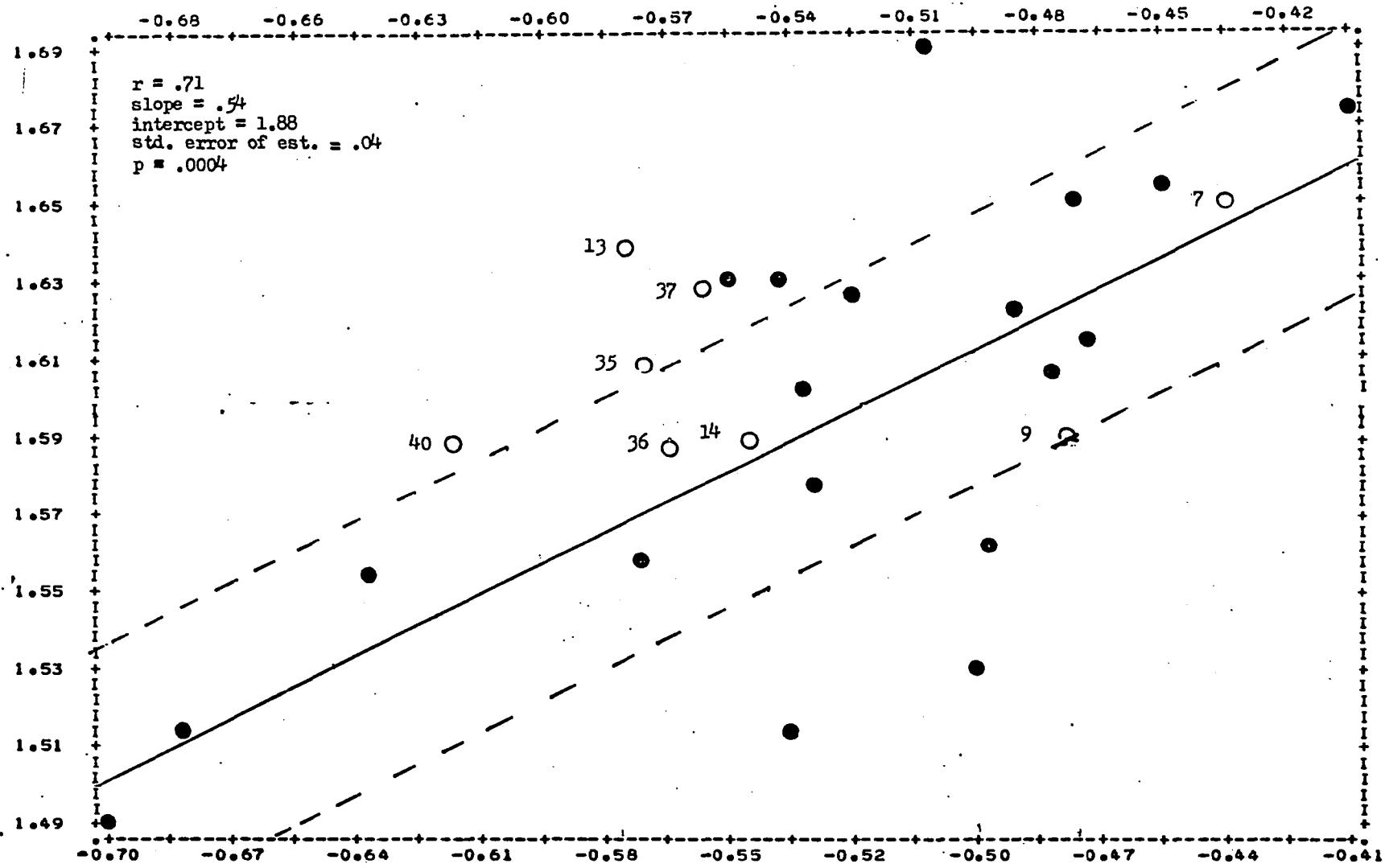


Figure 3: Scattergram of points for regression of nonbasal heat production (kcal/day) on body weight (kg). Filled circles represent normal animals (n=19) on which regression equation was based. Open circles are LH animals' post lesion data. Dashed line represents standard error of estimate.

LOG KILOCALORIES / DAY



LOG KILOGRAMS BODY WEIGHT

do not differ in any consistent manner from the normal animals' regression line. Within the range of body weights in the present experiment (.280 to .400kg) $\text{kg}^{.75}$ is approximately a linear function of kg ($r = .994$) however.

Activity measures

Figures four through eight depict the pre- and postlesion running wheel data for all animals. The data was plotted separately for days when they were not disturbed in the morning. The data points represent the log of the total number of revolutions run during each daily 18h period of darkness. The alternate day plotting of the data was done because it was apparent that some of the animals (e.g. CDF01, CDF04, CDF35) ran less in the night when they had been handled that morning.

The data clearly indicate that LH lesions resulting in chronic weight loss do not necessarily produce decreases in spontaneous wheel running (e.g. Gladfelter & Brobeck, 1962; Gladfelter, 1971). For only one animal (CDF40, fig. 8) was there a clear effect of the lesion on running (-27%). Several other animals showed a slight decrement (CDF07, CDF14, CDF35, CDF37), but others (CDF09, CDF13) appeared to run more during the postlesion phase, despite a 14.6% and 20.8% decrement in body weight for CDF09 and CDF13 respectively.

Stabilimeter Data

The stabilimeter data $(\bar{X} \text{ counts} / \text{trial} + 0.50)^{.50}$ is presented in fig. 9. There was a general trend for the animals to become less active over trials during the prelesion phase. Because of the small size of the dessicator, the animals acclimated to it quickly. Typically an animal would go to sleep for varying lengths of time after the start of a session. The postlesion period resulted in slightly elevated

Figure 4: Activity wheel data for CDF01, CDF02 and CDF03. Squares represent days when animals were handled in the morning. Triangles represent days when the animals were undisturbed. Plotted points are log of total amount of running during the 18 hour daily dark period.

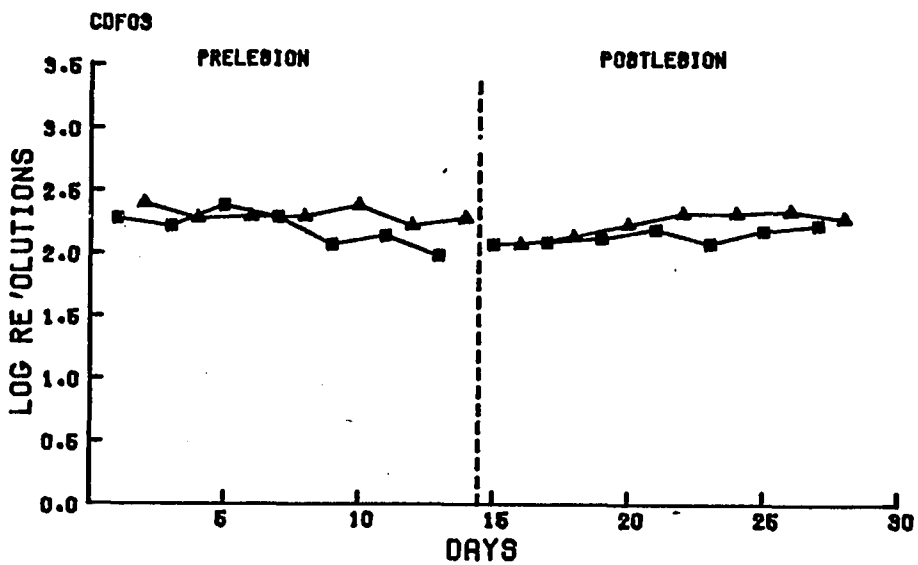
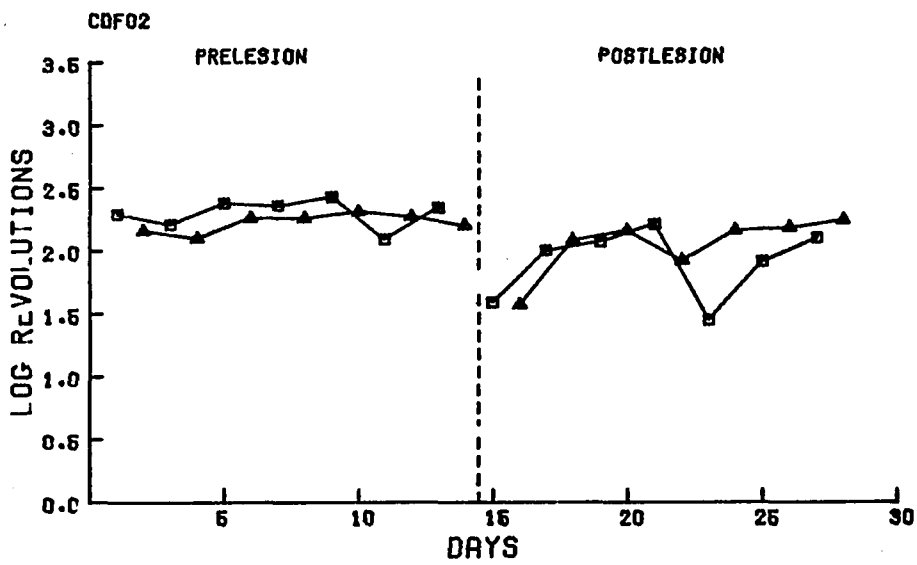
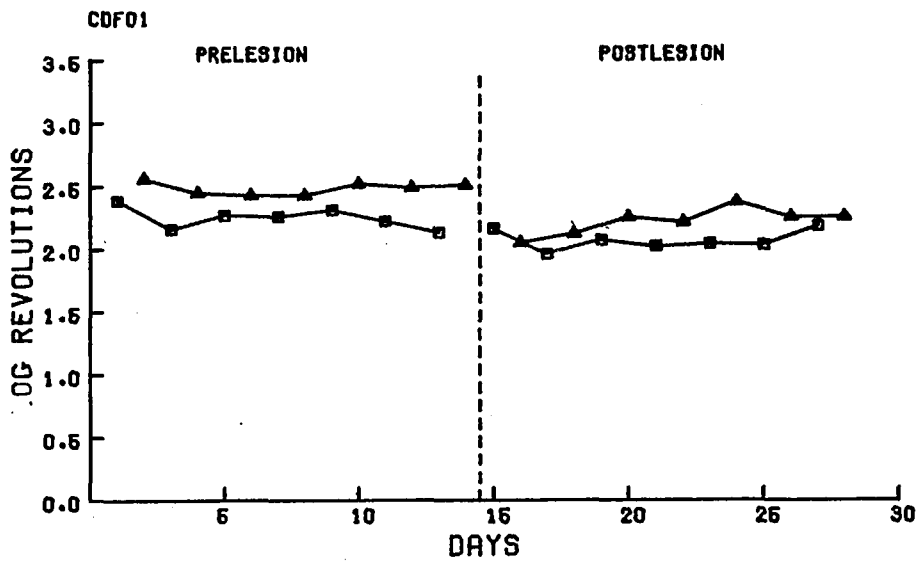


Figure 5: Activity wheel data for CDF04, CDF05, and CDF06. Squares represent days when animals were handled in the morning. Triangles represent days when the animals were undisturbed. Plotted points are log of total amount of running during the 18 hour daily dark period.

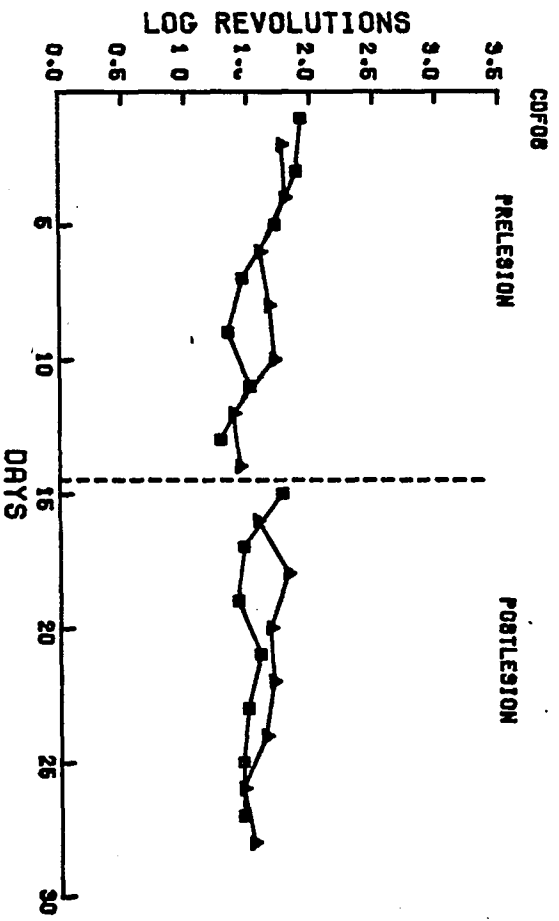
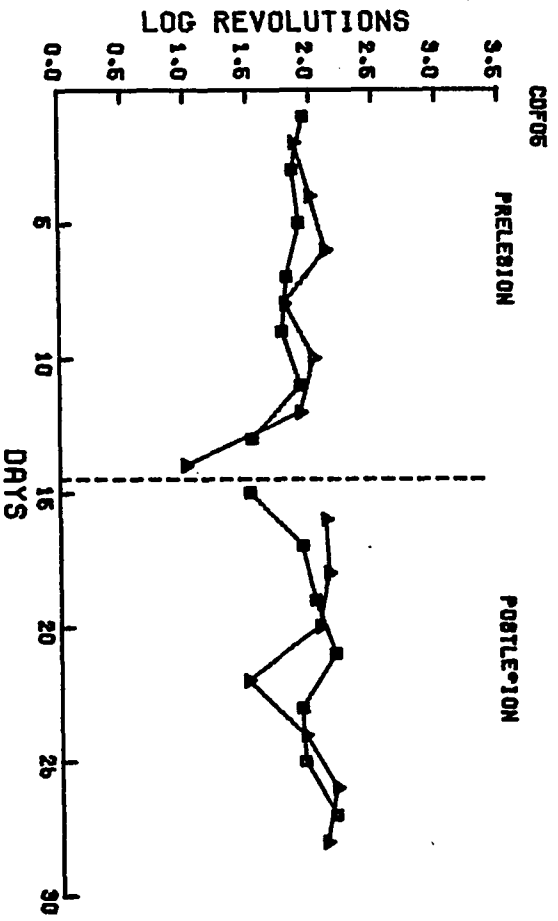
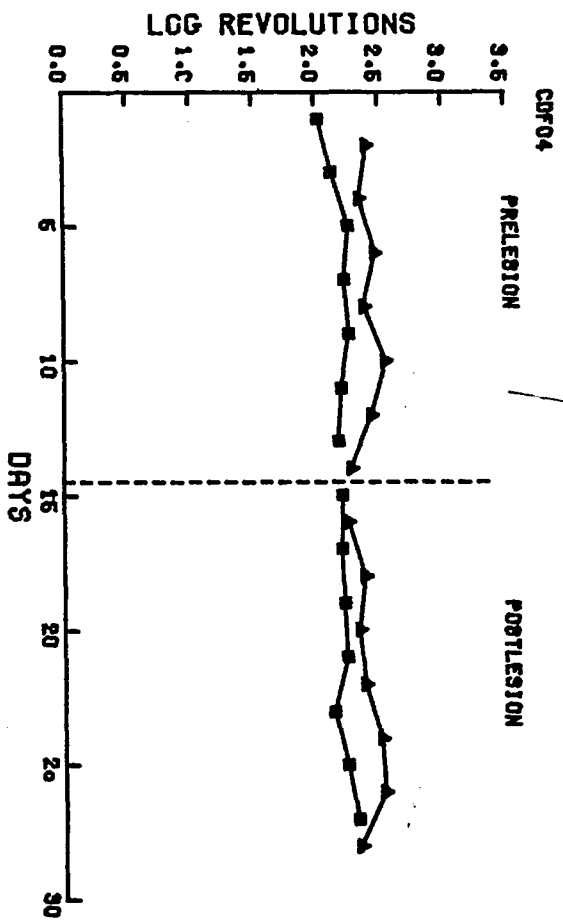


Figure 6: Activity wheel data for CDF07, CDF09 and CDF13. Squares represent days when animals were handled in the morning. Triangles represent days when the animals were undisturbed. Plotted points are log of total amount of running during the 18 hour daily dark period.

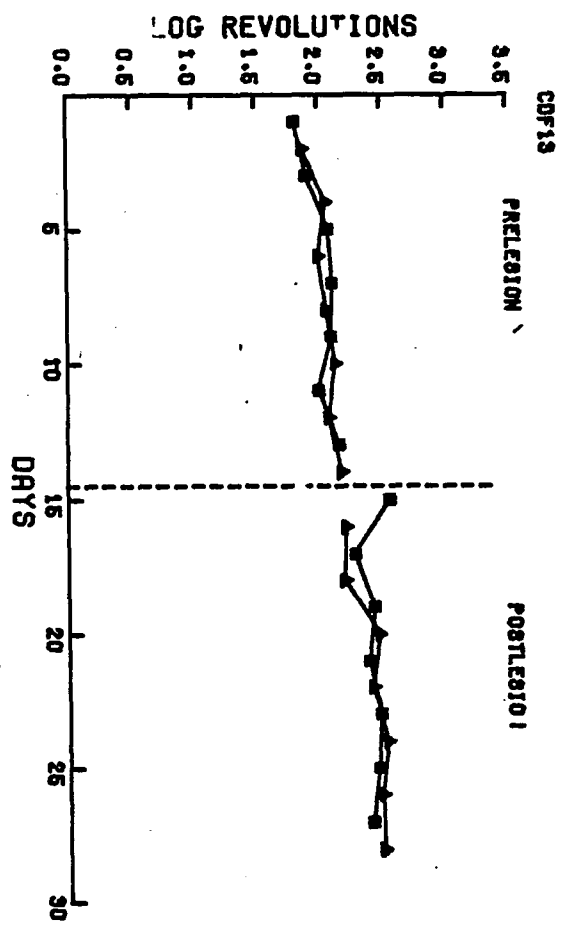
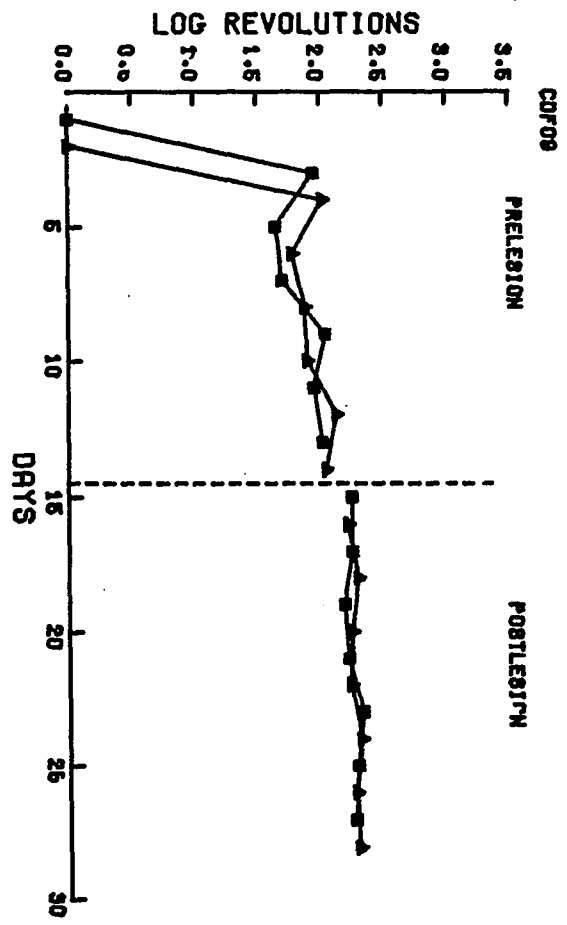
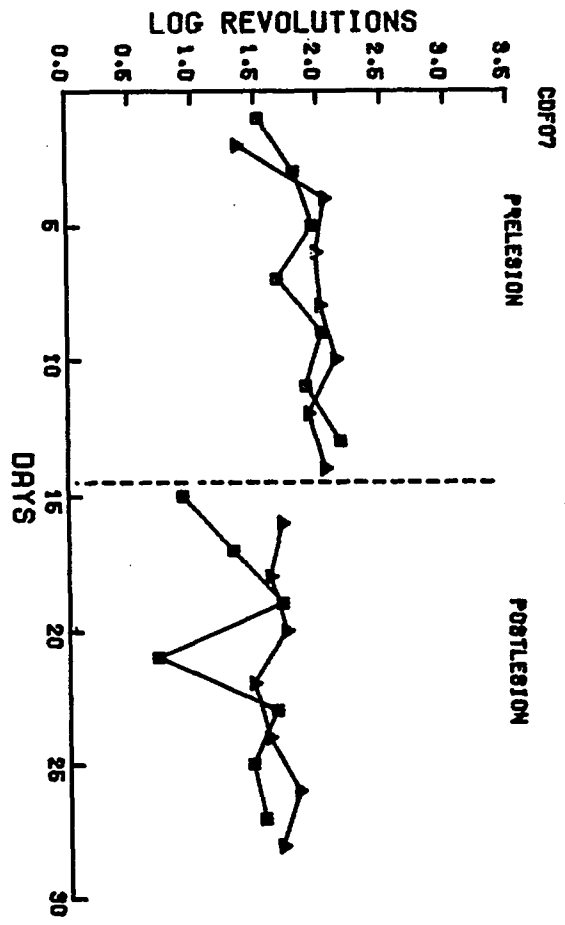


Figure 7: Activity wheel data for CDF14, CDF35 and CDF36. Squares represent days when animals were handled in the morning. Triangles represent days when the animals were undisturbed. Plotted points are log of total amount of running during the 18 hour daily dark period.

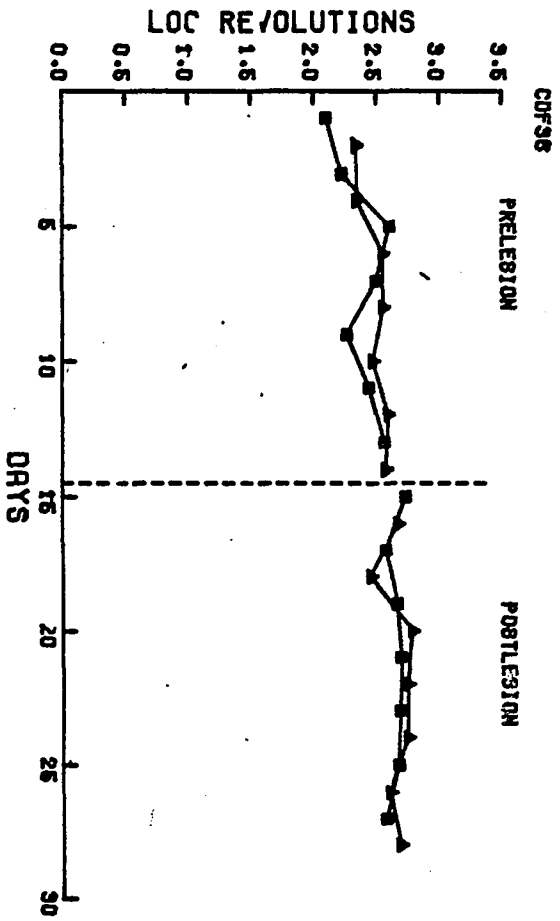
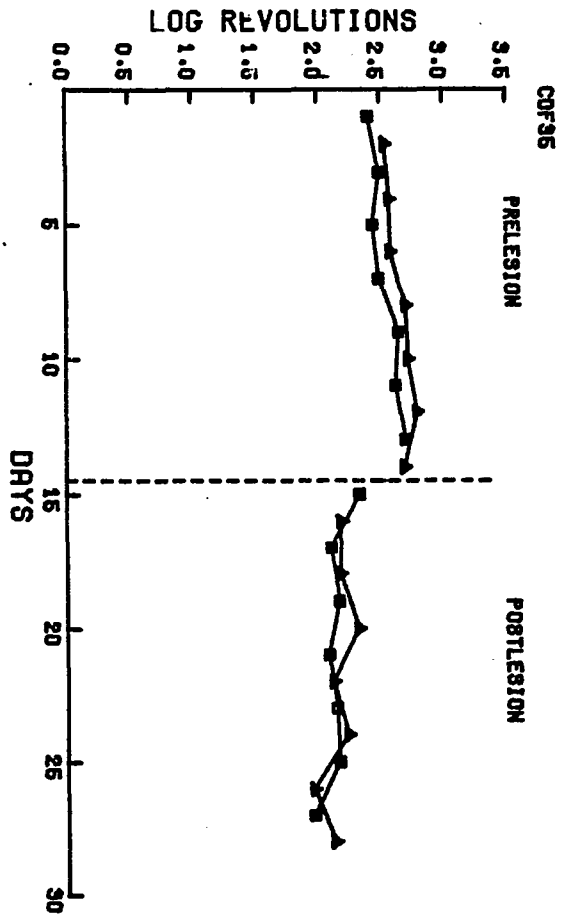
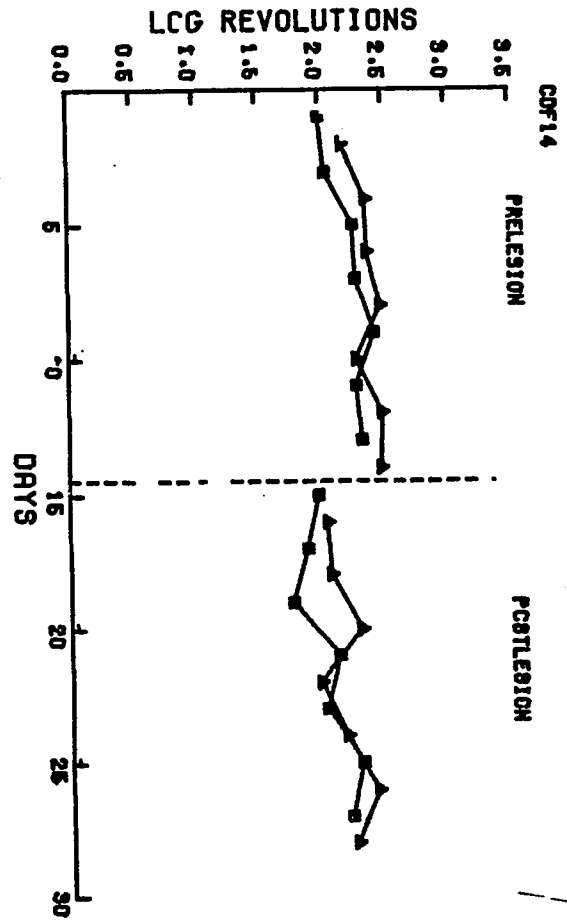


Figure 8: Activity wheel data for CDF37 and CDF40. Squares represent days when animals were handled in the morning. Triangles represent days when the animals were undisturbed. Plotted points are log of total amount of running during the 18 hour daily dark period.

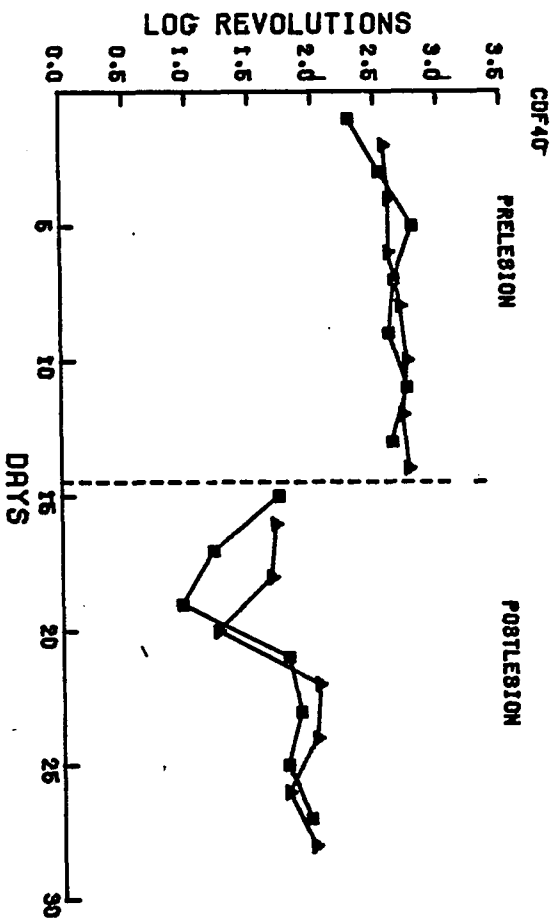
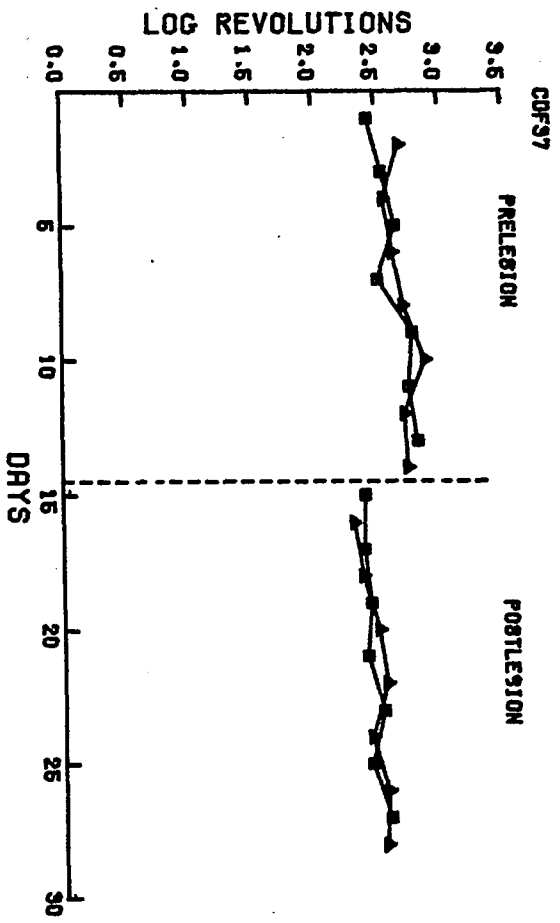
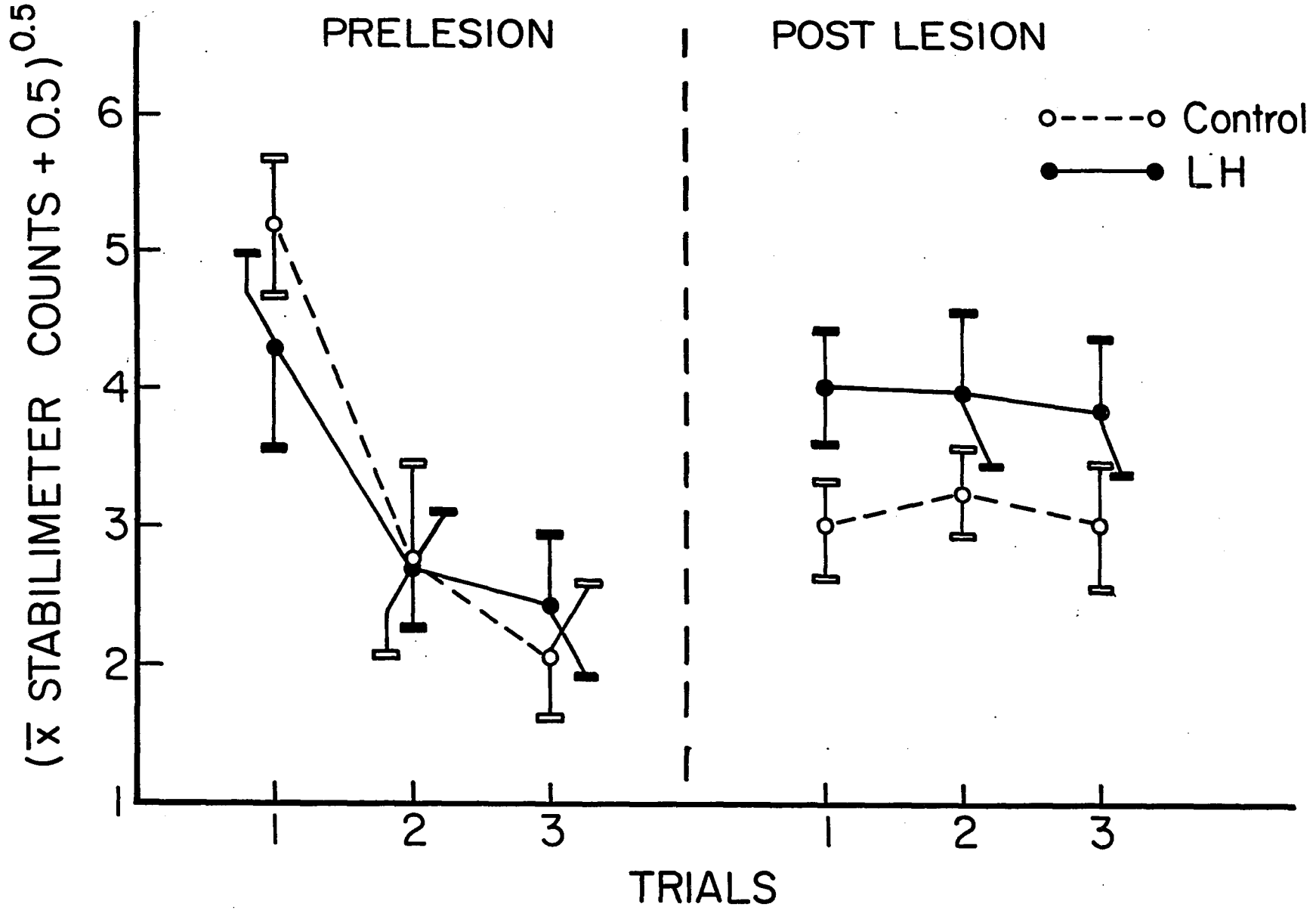


Figure 9: Stabilimeter data for all animals, for three prelesion and postlesion trials. Vertical lines represent standard error of the means.



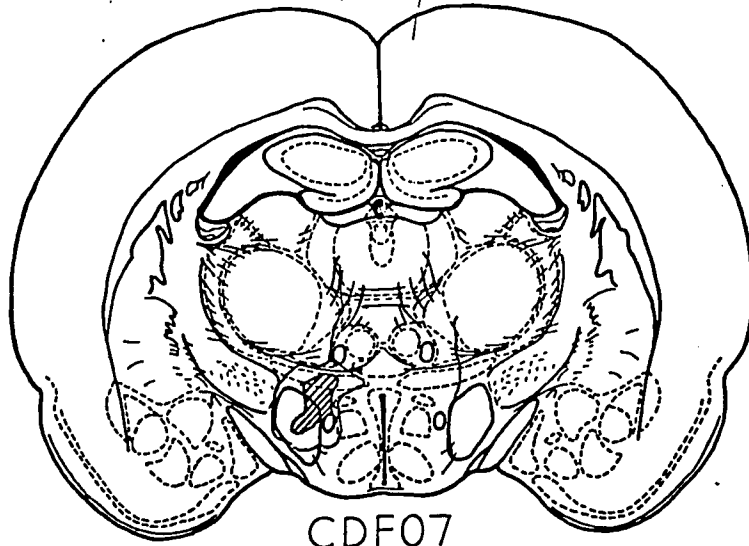
amounts of activity for both groups, with the LH animals more active than controls. This between groups difference was not statistically significant however as indicated by the overlapping standard errors of the means in figure nine. A nonsignificant t value was obtained between the only two means that did not have overlapping standard errors (postlesion trial 1).

Histology

The results of the histology show that all of the LH animals had lesions in the medial perifornical area (figs. 10-12). In most of the animals, the fornix was actually interrupted bilaterally. The lateral extent of the lesions included only minimal involvement of the medial internal capsule, and the foci of the lesions (striped area) never came in contact with this structure. All lesions were centered at about the level of plate 32 in König and Klippel (1963) atlas. All lesions were fairly symmetrical, except for CDF07, who appeared to have sustained only unilateral damage.

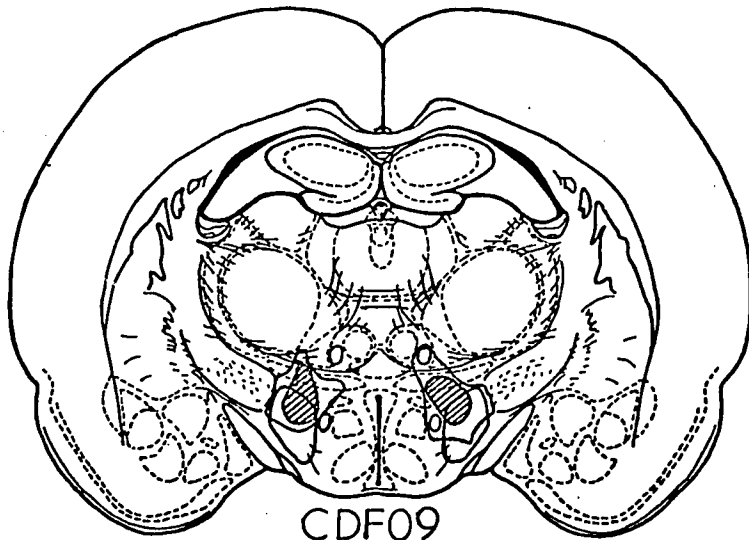
The control animals that had current passed during surgery (CDF02, CDF04, CDF05 and CDF06) sustained very minimal damage, with no clear focus, or if there was a focus, it was about the size of an electrode tract. Their placements were also more anterior to plate 32, and therefore out of the LH syndrome locus. Their histology is therefore not presented.

Figure 10: Approximate lesion centers for CDF07, CDF09 and CDF13. Numbers to the right of drawings represent the plate number and anterior-posterior distance according to the rat brain atlas of König and Klippel (1963). Lesion damage is outlined, main focus of damage is represented by striped areas.



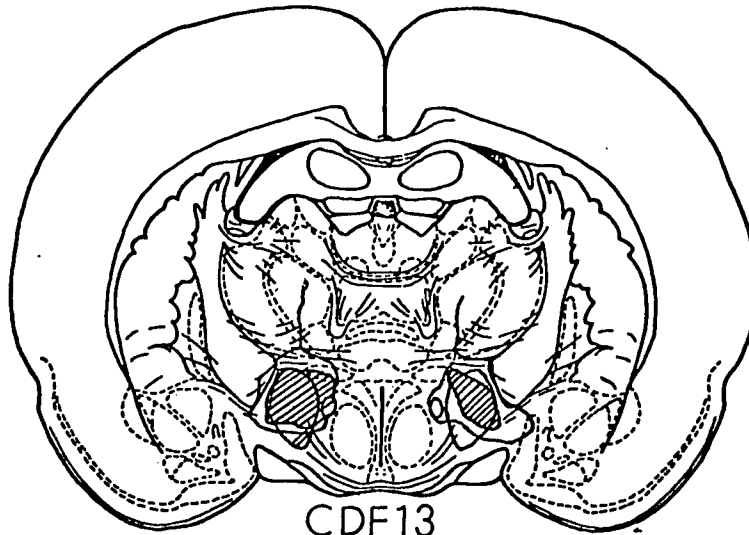
CDF07

FIG. 32b
A 4890 μ



CDF09

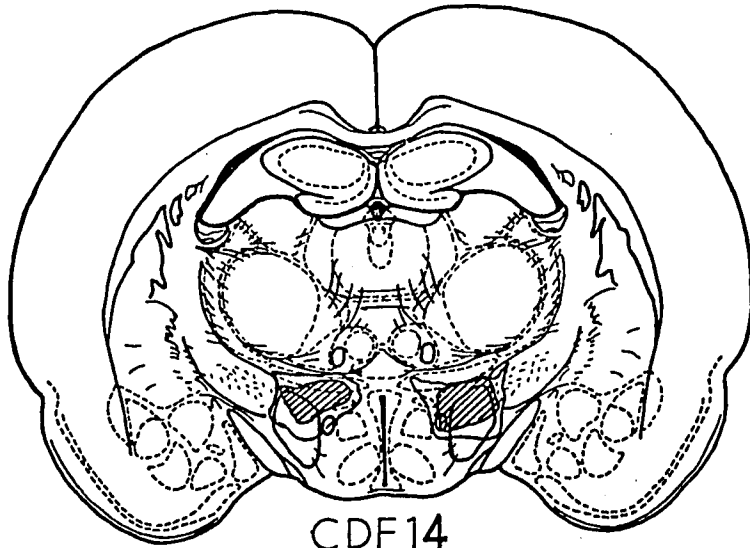
FIG. 32b
A 4890 μ



CDF13

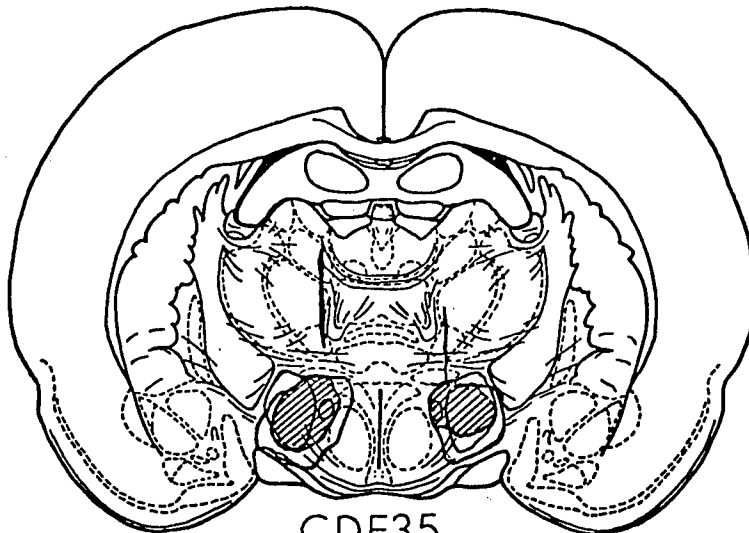
FIG. 30b
A 5340 μ

Figure 11: Approximate lesion centers for CDF14, CDF35 and CDF36. Numbers to the right of drawings represent the plate number and anterior-posterior distance according to the rat brain atlas of König and Klippel (1963). Lesion damage is outlined, main focus of damage is represented by striped areas.



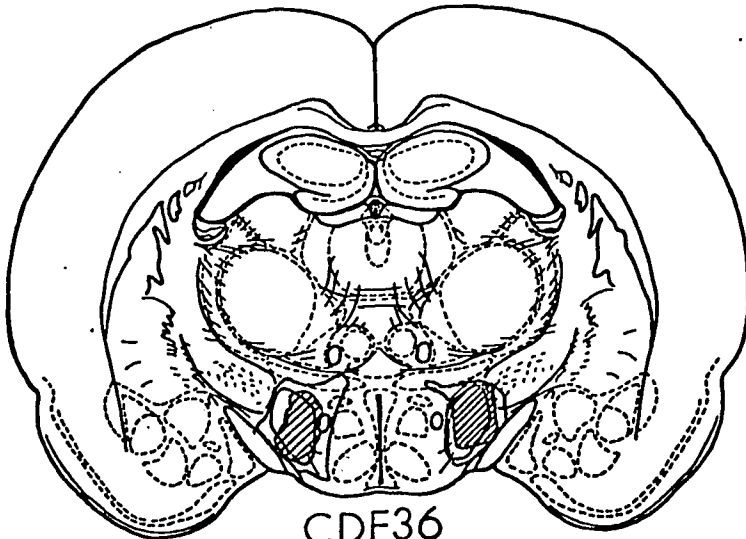
CDF14

FIG. 32b
A 4890 μ



CDF35

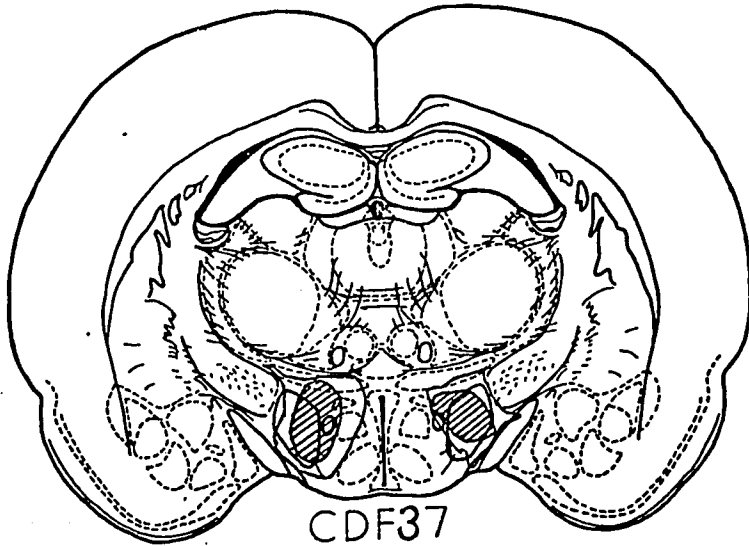
FIG. 30b
A 5340 μ



CDF36

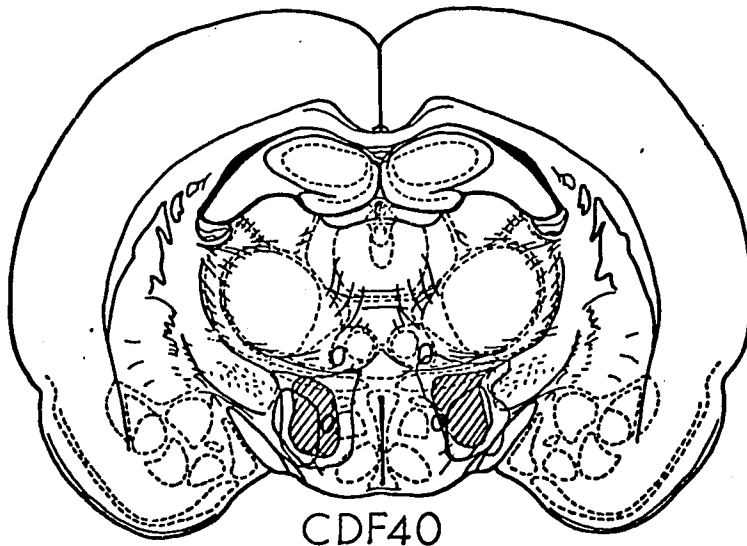
FIG. 32b
A 4890 μ

Figure 12: Approximate lesion centers for CDF37 and CDF40. Numbers to the right of drawings represent the plate number and anterior-posterior distance according to the rat brain atlas of König and Klippel (1963). Lesion damage is outlined, main focus of damage is represented by striped areas.



CDF37

FIG. 32b
A 4890μ



CDF40

FIG. 32b
A 4890μ

DISCUSSION

The results of this experiment clearly show that LH lesions do not always result in decreased spontaneous motor activity (Gladfelter & Brobeck, 1962; Gladfelter, 1971). These investigators have been repeatedly cited in the literature (e.g. Wayner, 1974; 1975), with their data being used as evidence indicating both a major role for the LH in mediating normal motor excitability and motor impairments in the LH syndrome (Morrison, 1968; Ungerstedt, 1974). However, these studies did not directly investigate activity changes in relation to the LH syndrome.

In the present experiment, only one animal showed a clear decrement in postlesion wheel running, and this was a small decrease compared to Gladfelter and Brobeck (1962) and Gladfelter (1971) who found almost no postlesion running. There appeared to be no relationship between postlesion weight loss, or time to recovery and postlesion running. CDF13 had the largest weight decrement and longest time to recovery, but his postlesion running appeared to be even greater than during the prelesion phase. Thus the results of this experiment extend the results of Balagura et al. (1969) who found a low correlation between severity of feeding deficits and their measure of hypokinesia. However, all of their lesioned animals showed a significant decrement in activity when compared to controls. They found that the hypoactivity was greatest for animals with damage to the posterior MFB. The stabilimeter data in the present study further shows that animals can display symptoms of the LH syndrome and not be hypoactive (fig. 9).

All LH lesioned animals in the present study exhibited postoperative behaviors that are associated with Teitelbaum and Epstein's

(1962) lateral hypothalamic syndrome. All LH animals had a chronic reduction in body weight (table 1), they tended to be hypodipsic (table 2) and early in recovery they appeared to be affected by the palatability of the diet that was offered. However, the overall severity of the symptoms, in terms of time to recovery (i.e. stage four) was shorter (table 2) than those reported by Epstein and Teitelbaum (1964; mode 2-4 weeks). Also, the animals were not prandial drinkers, they actually ate more food than the controls when deprived of water, indicating no impairment of salivary control (Kisseleff & Epstein, 1969). The lesion parameters in the present experiment produced smaller, more selective damage than Teitelbaum and Epstein (1962) and Epstein and Teitelbaum (1964), while still resulting in definable LH syndrome symptomatology.

The discrepancy between the previous findings (e.g. Gladfelter & Brobeck, 1962; Gladfelter, 1971) and those of the present experiment might be due to the size and/or location of the lesions. In both of Gladfelter's experiments, larger lesions (1.25-2.00 ma for 15 sec) were used, and the lateral lesions were centered more posteriorly, at about the level of the caudal ventromedial nucleus (plate 37 in König & Klippel, 1963). These lesions therefore probably impinged upon the medial internal capsule before the NSB fibers turned towards the striatum. The lesions in the present experiment (figs. 10-12) show that all LH animals had damage to the MFB. The lesions tended to be centered at about the level of plate 32 in the König and Klippel (1963) atlas, and therefore, the lesions that came in contact with the internal capsule, probably did so after the main component of NSB dopaminergic fibers turned towards the globus pallidus and striatum.

An important role for these central DA fibers in both the LH syndrome (Oltmans & Harvey, 1972, 1976) and motor activity (Ungerstedt, 1974) have been suggested. Ungerstedt (1974) observed that the reports of motor abnormalities associated with the LH syndrome always occurs in their animals who have had chemical (6-hydroxydopamine, 6-OHDA) lesions restricted to the NSB. In one study reported by Ungerstedt (1974), animals having a complete degeneration of striatal dopamine showed an aphagia and adipsia from which they did not recover after three to four months, and were cataleptic, akinetic and rigid. He points out the obvious parallels between these animals and the Parkinson syndrome in man. It is likely however, that such a drastic motor disturbance would preclude many behaviors, including feeding.

It is possible therefore, that the reports of motor impairment, particularly the results of Gladfelter and Brobeck (1962) and Gladfelter (1971), that have been associated with the LH syndrome are due to disruption of the ascending dopaminergic nigrostriatal bundle. The data of Balagura et al. (1969) are consistent with this since they found the most severe motor disfunction to be associated with their more posterior lesions. The use of smaller, more restricted lesions in the present experiment has shown that the effects on motor activity and weight regulation resulting from LH lesions can be clearly differentiated. Without accompanying biochemical analyses, it can not be stated unequivocally that the results reported here were due to NA involvement and a sparing of the DA system. According to the Cholinergic-CA atlas of Jacobowitz and Palkovits (1974), the lesions appeared to involve dorsal NA ascending fibers and cholinergic fibers and cell bodies in the dorsal fornical area and zona incerta. Finally, the fact that the animals in this experiment were not prandial drinkers further supports this contention. Oltmans

and Harvey (1972, 1976) found that the destruction of the NSB appeared to be crucial for the water regulation deficits seen in LH lesioned animals to occur.

The hypothesis that the LH lesioned rats sustaining weight loss would also have a reduced rate of oxygen consumption (Davis, 1977) was not supported (tables 3,4; figs. 2,3). In fact, both the LH and control animals had slightly elevated metabolic rates post surgically (13.48 vs. 12.60 ml O₂/min/kg^{.75}). While this increase was small (6.5%), it does represent a significant difference. Age was probably not responsible for the higher metabolic rates, since Johnson, Ward and Kibler (1966) found that there was only a slight decrease in metabolic rate in their rats due to age. Four of the control animals actually did sustain lesions. The damage was very small, however, and fell outside the LH syndrome site, being more anteriorly placed. The damage that was done, however minimal, might have accounted for the post surgical change. However, CDF01 and CDF03 were "full sham" operated, having only an electrode inserted and removed bilaterally. Referring to table 3, it can be seen that these animals also had slightly increased rates of oxygen consumption (about 3.4%). Morgane (1961b) has shown that such full sham procedures can affect food and water intake, and when more laterally placed can produce metabolic changes. It is possible then that the slight metabolic change may have been due to disturbances caused by electrode tract damage. It would have been informative in this case to have included unoperated control animals in the present experiment as well.

The metabolic rate data are interesting in light of previous reports of metabolic abnormalities after LH lesions (Morgane, 1961a,b; Stevenson & Montemurro, 1963; Morrison, 1968). Each of these investigators found evidence for short term increases in metabolic rate for their LH lesioned rats. Morgane (1961a,b), using small,

selective lesions including the full sham procedure determined that the metabolic alteration was associated with far lateral (i.e. pallidofugal, NSB) damage. Morrison (1968) found an increase after seven days post operatively only in animals that remained completely aphagic for up to ten days, at which time the animals were sacrificed and no more metabolic determinations made. The results of the present experiment indicate that there might be a longer term metabolic increase. The time from surgery to the measurement of metabolic rate was as long as three months. Unlike Morrison's (1968) animals however, all LH animals in the present study recovered to the point where they could maintain themselves on dry food and tap water. Finally, the metabolic data is consistent with Gladfelter's (1971) results. He studied the effects of large and small lateral and medial hypothalamic lesions on running wheel activity and endocrine function. His activity data replicated the earlier work of Gladfelter and Brobeck (1962) and the endocrine measures showed no anterior pituitary deficiencies with the lateral lesions. He did find however that the lateral hypothalamic lesioned animals had significantly larger thyroid glands after administration of propylthiouracil. This finding might indicate a hyperactivity of TSH secretion following the lesions. No direct measure of metabolic rate was taken however.

The failure to find a metabolic impairment, while consistent with Gladfelter's (1971) data, is in disagreement with the results reported recently by Davis (1977). The results of Halász (1972) and Ganong (1972, 1974) should predict that the disruption of ascending NA input to the HTA would result in altered endocrine functioning. In further support of this, Morgane (1975) has observed that ..

anatomically, collaterals from path neurons, as well as the MFB itself sends impulses to nuclei in the medial hypothalamus. Therefore, either directly, or indirectly by a medial relay nucleus, the MFB provides input to wide areas of the tuberal zone (including the HTA) of the hypothalamus, and therefore, no doubt influences anterior pituitary functioning (p. 45).

The lack of a metabolic impairment for the animals in the present study might be related to Stricker and Zigmond's (1976) observation that catecholamine pathways can sustain extensive damage before basal function is disrupted. The reason for this is in the nature of the compensatory mechanisms available to CA neurons. For example, a doubling of NA turnover in undamaged neurons after lesioning has been observed. Coupled with increased sensitivity (e.g. "denervation supersensitivity") of the post synaptic receptor sites that occurs after lesions (e.g. five-fold increase for DA), Stricker and Zigmond (1976) estimate that as much as 90% of the CA fibers can be destroyed before permanent functional change occurs. It is therefore possible that enough residual tissue remained to sustain the metabolic rates of the animals in the present experiment.

Another variable that may have accounted for the failure to find any metabolic impairment is the extended dark period (18 hours) to which the animals in the present study were exposed. Bakke and Lawrence (1965) have shown that TSH secretion exhibits a clear circadian periodicity for animals on a 12 hour light/dark cycle. The highest values of TSH output occurred at night with the lowest output between the hours of 12 and 1 PM. Stricker and Zigmond (1976) have observed that the capacity of central CA neurons for neurotransmitter release may be much greater in the dark than during the daylight hours.

It is interesting that Gladfelter's (1971) animals were on a light/dark cycle with only 8 hours of light per week and he found no metabolic impairment for his animals sustaining LH lesions. Thus the extended period of darkness may augment the CA fiber's normal compensatory mechanisms. Finally, Harrell and Balagura (1975) found an amelioration of the motor deficits that they observed in their LH lesioned animals when they were exposed to five days of constant darkness prior to surgery. While these results are at variance with Gladfelter's (1971), the role of such environmental factors might be important. No investigations have been carried out to determine the effect of this variable on the chronic reduction in body weight that occurs with LH lesioned animals however. Because of the importance of monoamine metabolism for the behavioral and possibly metabolic symptoms of the LH syndrome, this variable might be of importance to include in future studies.

Finally, the discrepancy between the results reported here and those of Davis (1977) might be due to the use of different strains of rats. The animals in the present experiment were essentially at their asymptotic body weights at the time of surgery, while those used by Davis (1977) were still growing rapidly. Thus, the neuroendocrine system may be more susceptible to disruption in the rapidly growing organism compared to one that has achieved its stable adult body weight. Therefore, this variable might also be of importance to consider in future investigations.

The results reported in this experiment provide further evidence that LH lesioned animals do not exhibit a unitary invariant "syndrome" (Morgane, 1961a, 1961b, 1975). Besides the lack of a decrement in spontaneous locomotor activity, the animals in this study

were not prandial drinkers, the LH animals actually ate more food in the absence of water than the controls. Disruption of neurochemically dissimilar fiber tracts (e.g. NSB, MFB) probably contribute different aspects to the postlesion behaviors of these animals. The extent to which certain symptoms always occur and accompany other symptoms is not known. Part of the problem is the lack of specificity of electrolytic lesions in such a neuroanatomically and neurochemically diverse area as the LH. More selective destruction of the different fiber pathways is needed to answer the question of their relative contributions to the LH syndrome, endocrine function and behavior in general. Recent advances in more specific transmitter neurotoxins (e.g. 6-OHDA; Ungerstedt, 1974; Stricker & Zigmond, 1976) may eventually provide the necessary specificity to determine the relative importance of the different amine systems to behavior. Until then, the use of large electrolytic lesions (e.g. Teitelbaum & Epstein, 1962; Gladfelter & Brobeck, 1962) will probably not provide much new information and may even obscure important relationships between these systems in the hypothalamus.

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