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THE EFFECT OF LOCUS COERULEUS LESIONS ON FEEDING BEHAVIOR IN RATS

by

JEFFREY M. HALPERIN

A dissertation submitted to the Graduate Faculty in Psychology in partial fulfillment of the requirements for the degree of Doctor of Philosophy, The City University of New York.

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Abstract

THE EFFECT OF LOCUS COERULEUS LESIONS ON FEEDING BEHAVIOR IN RATS

by

Jeffrey M. Halperin

Adviser: Professor Steven J. Ellman

A review of the feeding literature indicates the existence of at least two, anatomically, neurochemically, and functionally distinct neural mechanisms involved in the regulation of feeding behavior; a feeding mechanism, and at least one satiety mechanism. As opposed to earlier suggestions that these mechanisms were controlled solely by feeding centers in the hypothalamus (HYP), recent data indicate that fibers ascending to the HYP play a major role in their regulation. It is more likely that the HYP is the focal point of several food regulating systems in the brain.

Much converging evidence indicates that the paraventricular nucleus of the HYP (PVN) plays a central role in the regulation of feeding. Data also indicate that the role of the PVN in the regulation of feeding is noradrenergically (NA) mediated (Leibowitz, 1976). HYP NA innervation ascends almost entirely from nuclei in the hind-

brain (Ungerstedt, 1971). Therefore, destruction of NA nuclei or pathways crucial to PVN innervation, should result in alterations in feeding.

Destruction in the area of the ventral NA bundle (VNB), which is the major NA pathway innervating the HYP, has been found to result in hyperphagia (Ahlskog & Hoebel, 1976; Gold, 1973). Although these lesions significantly reduce HYP NA, the amount of depletion does not correlate with the magnitude of the hyperphagia.

It is suggested that the NA mediating the hyperphagic behavior is not from the VNB, but rather an innervation of smaller magnitude, to discrete nuclei (i.e., the PVN). Thus, alterations in feeding behavior would be due to small, discrete, NA depletions and would not be correlated with overall HYP NA levels. Furthermore, if this innervation ascends to the HYP through a pathway in close proximity to the VNB, it would be difficult to sever it without causing damage to the VNB. Therefore, destruction to this pathway is likely to result in large NA depletions in the HYP that are not correlated with the magnitude of the hyperphagia.

Based upon data indicating that (a) the intermediate bundle (Maeda & Shimizu, 1972), which ascends from the area of the LC, terminates in the HYP, and (b) lesions to the LC region selectively decrease NA in the PVN, I suggest that the intermediate bundle, rather than the VNB, is the source of the NA innervation whose disruption results in hyperphagia.

Experiment 1 examined the effects of bilateral LC lesions on feeding behavior in rats that were maintained on a sweetened milk

diet. Beginning approximately one week after the lesions, the LC-lesioned rats became hyperphagic as compared to both lesioned and unlesioned controls.

Experiment 2 examined the effects of ventral LC lesions on feeding behavior in rats maintained on a solid food diet. These animals also became hyperphagic as compared to lesioned and unlesioned controls. Histological analysis revealed that the critical area involved in the hyperphagia is the subcoeruleus.

The hyperphagia did not appear for approximately one week after the lesions. This suggests that the hyperphagic response is being mediated in the brain some distance from the lesions. This time duration, which probably reflects the time required for axonal degeneration, is equivalent to the time it is believed to take for NA reductions to occur in the HYP following LC lesions.

It is suggested that the intermediate bundle, rather than VNB destruction, may be responsible for some hyperphagic syndromes. The data is also discussed in terms of its implications as to the function of REM sleep.

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Table of Contents

List of Appendices

List of Tables

List of Figures

These studies were designed to explore the relationship between dorsal brainstem structures in the area of the locus coeruleus (LC) and the regulation of feeding behavior. Early research examining the neural regulation of food intake concentrated almost entirely upon the hypothalamus (HYP) in which the "feeding and satiety centers" were believed to be located. Recent research has indicated, however, that the neural circuitry involved in the regulation of feeding extends beyond the HYP. In fact, the HYP's role in feeding may be mediated, at least in part, by inputs from hindbrain structures.

Normal Patterns of Food Intake

Careful analyses have been performed on the feeding patterns in animals with the hope of enhancing the understanding of food intake regulation. It has been found that most mammals feed periodically, in discrete meals. LeMagnen (1971) found that the meal size in rats, allowed free access to food, is highly correlated with the duration of the subsequent intermeal interval (IMI). The duration of the IMI, however, does not predict the size of the following meal. Therefore, eating a large meal will increase the time until the next meal, but a long period between meals does not necessarily terminate with a large meal.

This data suggests that separate mechanisms are involved in the initiation and maintenance of feeding. Since the amount consumed during a single meal is independent from the duration of the preceding IMI, it is unlikely to be regulated by physiological "need." The onset time of a meal, however, is determined by the size of the previous meal. This indicates that it is regulated by need. It is likely that hunger is required to initiate feeding, and therefore, a determinant of meal

frequency, while meal size is regulated by a separate satiety mechanism.

Alterations in food intake must occur through the change of either meal frequency or meal size. Data indicate that meal frequency and size alterations occur independently of each other. Various environmental manipulations which alter food intake, differentially effect meal size and frequency. Meal frequency increases in response to cold stress (more energy required to maintain body temperature) while meal size remains unchanged (Kissileff, 1968). Conversely, meal size increases in response to food deprivation (Levitsky, 1970), caloric dilution of the diet (Snowdon, 1969), and lactation (Kissileff & Becker, 1974), while meal frequency remains unaltered.

Food-energy regulation in this manner is highly adaptive when food is not available regularly or when feeding brings a specie into a dangerous environment. Large amounts of food consumed during a single bout can maintain an animal for long periods of time. If, on the other hand, meal size was determined by the IMI, irregularly available food would frequently result in waste because of reduced hunger.

Neurophysiological and neurochemical research examining the regulation of feeding behavior have also indicated the likelihood that two separate mechanisms are involved in the regulation of feeding; a hunger mechanism and a satiety mechanism.

The Lateral Hypothalamus

Electrical stimulation and lesion manipulations in the area of the lateral HYP (LH) result in dramatic alterations in feeding behavior. Lesions to this area result in aphagia (Anand & Brobeck, 1951) while stimulation

elicits eating (Anand & Dua, 1955). Based primarily on these findings, the LH has frequently been referred to as the "feeding center" in the brain.

Stimulus bound eating. Electrical stimulation to various loci within the LH have been found to elicit feeding in satiated rats. This feeding, frequently referred to as stimulus-bound eating (SBE), has many behavioral similarities to normal (hungry) feeding. SBE is taste responsive, goal directed and motivated feeding. With the onset of stimulation, animals will eat only if certain foods are available (Valenstein, Cox & Kakolewski, 1970). If stimulation occurs in the absence of food, motor responses associated with feeding do not occur (Valenstein et al., 1970). If, however, food can become available by performing a task, rats will rapidly learn to work to obtain access to the food when the stimulation is initiated (Coons, Levak & Miller, 1965; Miller, 1957; Morgane, 1961). SBE is also inhibited by d-amphetamine (AMPH) as is normal feeding (Miller, 1960).

Controversy exists as to the specificity of a pure feeding center in the LH. Other motivated behaviors such as drinking, copulation, aggression, grooming, gnawing and nest building have been elicited by LH electrical stimulation (for review, see Valenstein, Cox & Kakolewski, 1969). Different loci within the LH have been found to be more likely to elicit specific behaviors, however, there is much overlap.

Valenstein et al. (1970) reported data indicating that a single electrode can elicit several different stimulus-bound behaviors (SBB). According to them, the behavior that is elicited is dependent upon the past experience of the subject and which goal object is most readily available. He reports that minor goal object alterations such as changing

the shape of the food dish, can abolish SBE. Further support for his "plastic system" hypothesis is that no precise anatomical locus has been found that reliably elicits only one SBB.

In opposition to Valenstein's hypothesis, Wise (1968) suggests that there is anatomical site-specificity for each SBB. He believes that specific motivational systems are closely interwoven, but anatomically distinct. With repeated trials of SBE within an animal, Wise found a lowering of the threshold required to elicit the feeding response. He explains Valenstein's elicitation of several behaviors from one electrode (during which the same current was used) as being due to current spread and a lowering of thresholds for anatomically adjacent behaviors. Data indicating that SBE and stimulus-bound drinking can be differentially manipulated using pharmacological agents lends support to Wise's "fixed system" hypothesis (Grossman, 1960).

Other evidence indicating the site-specificity and motivated nature of SBB is that almost all electrodes that elicit SBB, also support intracranial self-stimulation (ICSS) (Margules & Olds, 1962). The presence of food enhances ICSS rates from electrodes that also elicit SBE, while sex hormone manipulations do not (Coons & Cruce, 1968; Gallistel & Beagly, 1971). Conversely, the presence of an estrous female increases ICSS rates in male rats whose electrodes have been found to elicit copulatory behavior (Caggiula & Hoebel, 1966).

Steiner and Ellman (1972) have hypothesized the existence of an ICSS neural network which subserves general motivated behavior. Within this hypothesized network, they suggest that there are distinct areas for specific motivated behaviors which should elicit SBB (Ellman & Steiner, 1974). They also hypothesized that nuclei in the hindbrain (possibly noradrenergic)

are responsible for maintaining this network.

Steiner and Ellman's hypothesis is supported by data indicating that electrical stimulation to loci caudal to the HYP can also elicit SBB. Furthermore, lesions to HYP SBB sites do not alter the elicitation of that behavior from more caudal loci, but lesions to caudal SBB loci block HYP elicited SBB (Bernstein & Micco, 1976). Additional support for their hypothesis is that hindbrain lesions have been reported to abolish ICSS in some HYP loci (Farber, Ellman, Mattiace, Holtzman, Ippolito, Halperin & Steiner, 1976).

The LH aphagia syndrome. Bilateral lesions to the LH result in a syndrome characterized by aphagia and adipsia (Anand & Brobeck, 1974). It was found, however, that with careful nursing and tube feeding, to keep the animals alive, recovery would eventually occur (Teitelbaum & Stellar, 1954). This recovery has been found to follow a regular four stage course over a period of several months. During the first stage, immediately following the lesions, no feeding or drinking occurs. If food is presented, the animal actively avoids it. During the second stage, the animal begins to eat wet, palatable foods, but will not eat dry food or drink water. The third stage is characterized by eating and caloric regulation, but the animal remains adipsic. During the final stage, the rats begin to drink water again. Although these rats appear normal, sensitive tests reveal deficits in water regulation. They are highly sensitive to the taste of water and they do not respond to intraperitoneal saline alterations. These "recovered" rats appear to drink in response to a dry mouth, rather than dehydration. All of their water intake occurs during meals (Teitelbaum & Epstein, 1962).

Powley and Keesey (1970) have suggested a model to account for the aphagia and gradual recovery following LH lesions. They suggest that LH lesions lower the setpoint for the regulation of body weight. When the aphagic animals finally begin regulating their caloric intake, they do so at a new, lower level. To test this notion, they starved rats to drastically reduced body weights prior to LH lesioning. Subsequent to the lesions, these rats immediately began eating. They maintained their body weight at the same level as recovered LH lesioned rats that were not prestarved. Both of these groups maintained their weight at levels below unlesioned controls. The aphagia, according to Powley and Keesey, lasts only until the lower body weight is reached.

Teitelbaum (1971) accounts for the aphagia and subsequent recovery as the "encephalization" of feeding. He suggests that cortical areas take over the function previously regulated by the LH. In support of this notion, it was found that cortical depression, induced using potassium chloride, in recovered LH animals produces a long lasting suppression of feeding (Teitelbaum & Cytawa, 1965).

Some data indicate that the aphagia characteristic of LH lesions may be due to the disruption of dopaminergic (DA) mechanisms. In addition to resulting in aphagia, LH lesions cause severe sensory and motor deficits. The majority of lesions in aphagia cause destruction to the nigrostriatal bundle. This is a collection of DA fibers which ascends from the substantia nigra (SN). Electrolytic and chemical lesions to the SN result in severe motor deficits along with aphagia and adipsia (Ungerstedt, 1971). Other studies have shown that these lesions produce many symptoms characteristic of LH aphagia such as high taste responsivity and drinking only with meals (Fibiger, Zis, & McGeer, 1973).

A mild tail pinch has been demonstrated to induce feeding in satiated rats. Data indicates that this phenomenon is DA mediated; the effect is blocked by DA, but not noradrenaline (NA), antagonists (Antelman, Szechtman, Chin & Fisher, 1975). Tail pinching has been found to induce feeding in both LH and SN lesioned rats (Antelman, Rowland, & Fisher, 1976). This phenomenon, however, is not specific to feeding. In the presence of the appropriate goal object, tail pinching has also been found to elicit other goal directed behaviors such as aggression and copulation (Caggiula, 1972). It is likely that the stimulation of the DA system facilitates these behaviors by activating the motor systems necessary for their performance.

Other data has indicated that the cell bodies within the LH may not be the "center" responsible for the intergration and organization of feeding. Both Gold (1967) and Grossman (1971) reported that the transection of fibers entering the LH, which caused little or no cellular destruction, resulted in aphagia.

Zeigler and Karten noted that many fibers ascending from central trigeminal structures pass through the brain in the vicinity of both the LH and the SN. In a careful review of the literature, they noted that most lesions that result in aphagia and adipsia cause destruction to the trigeminal lemniscus. They suggested that lesions to this structure, which results in sensory deficits to the head, may account for at least some aspects of the LH syndrome. They found that large LH lesions in pigeons which spared the central trigeminal structures, had no effect on feeding behavior, while lesions of these structures results in hypophagia (Zeigler & Karten, 1973). Zeigler and Karten (1974) also found that lesions of the trigeminal lemniscus in rats, which spared the entire LH,

resulted in aphagia and adipsia. This syndrome, although similar to the LH feeding syndrome, had some differences. The aphagia and adipsia had a more rapid recovery, there was less motor debilitation, and the lesioned rats showed no aversion to food or water; if applied to their mouth they would lick. Although there are many differences between the two syndromes the similarities indicate that some aspects of feeding regulation are due to fibers ascending from more posterior loci.

The Ventromedial Hypothalamus

The ventromedial hypothalamus (VMH) has frequently been referred to as the "satiety center" in the brain. Early data that led to this notion is that mice injected with gold thioglucose (GTG) become hyperphagic and obese (Bracher & Waxler, 1949). The gold component of this chemical, which is toxic, is known to destroy brain cells. In the injected mice, it was found that the GTG became concentrated in the area of the ventromedial hypothalamic nucleus (VMN), where the cells were destroyed. It was hypothesized that these cells contained gluco-receptors, which were activated when glucose availability was high. The activity of these cells was believed to result in satiety. The GTG, it was then believed, was drawn to the glucoreceptors, and destroyed the satiety mechanism by killing the cells. Neither gold thiomalate nor gold thiogalactose produce this localized brain damage which indicates that these cells are sensitive specifically to glucose (Mayer & Marshall, 1956).

The special affinity of the VMH to glucose, however, has recently been questioned. It appears that GTG may be indirectly damaging the cells by destroying capillaries in the vicinity of the VMN (Arees, Veltman & Mayer, 1969).

Hypothalamic hyperphagia: behavior. Bilateral lesions to the VMH region result in a syndrome classically referred to as hypothalamic hyperphagia (Anand & Brobeck, 1951). This syndrome is characterized by extreme overeating and consequently, obesity.

Hypothalamic hyperphagia occurs in two phases (Teitelbaum, 1961). During the dynamic phase, which has been reported to begin within one day of the lesion, the animal eats two to three times its normal amount and gains weight very rapidly. This phase may last up to several months and results in rats weighing two to three times that of controls.

Subsequent to the dynamic phase is the static phase. During this time, food intake decreases to slightly above control levels, and body weight is maintained at a high level. If, during the static phase, a rat is starved to normal body weight, ad libitum eating results in the hyperphagia characteristic of the dynamic phase (Teitelbaum, 1961).

VMH-lesioned rats no longer maintain the diurnal cycle of food intake characteristic of normal rats; they eat at a relatively constant level throughout the day. When maintained on a liquid diet, the hyperphagia is characterized by an increase in meal size, while meal frequency remains unaltered. They begin eating the same number of times as normals and eat at approximately the same speed, but do not get satiated as fast (Teitelbaum & Campbell, 1958).

On a solid food diet, the hyperphagic rats eat slightly larger meals and more frequently. It was suggested that the increase in meal frequency is due to the bulk of solid food. Liquid diets are calorically more dense than solid food, therefore, rats cannot get as many calories per meal with a solid food diet, and must eat more meals. In support of this, it was found that HYP hyperphagic rats with surgically increased stomach capacities,

ate larger meals less frequently (Teitelbaum & Campbell, 1958).

Another characteristic of HYP hyperphagic rats is their apparent lack of motivation for food. They are extremely sensitive to dietary taste and texture variations. Small amounts of quinine adulteration in the food (which would hardly alter feeding in normal rats) result in a cessation of feeding. Miller, Bailey and Stevenson (1950) found that on a variety of operant (food-reinforced) tasks including bar pressing, running down an alley, and acceptance of foot shock, HYP hyperphagic rats performed worse than controls.

Miller et al. (1950) hypothesized that the VMH was the site in the central nervous system (CNS) which "turned off" feeding. They suggested that the mechanism that regulated short term satiety was impaired in HYP hyperphagic rats. Support for this hypothesis is that these rats eat more, appear less motivated for food (therefore, they are not hungry), and eat larger meals rather than more meals.

Much data has been accrued which make this hypothesis untenable. HYP hyperphagic rats do not have a short term satiety deficit. They respond to gastric loads (Smith, Salisbury, & Weinberg, 1961) and increased blood sugar levels (Reynolds & Kimm, 1965) with reduced food consumption. If the stomach capacity of the HYP hyperphagic rats is surgically reduced, they maintain the hyperphagia by eating more meals (Brooks, Lockwood & Wiggins, 1946). Finally, if these rats had only a satiety deficit, the increased meal size should result in decreased meal frequency.

Hoebel and Teitelbaum (1966) proposed that the nature of the defect was not in the regulation of food intake, but the regulation of body weight. Once the rats become obese, they stop overeating and regulate

calories to maintain their new weight. If static phase rats are starved, they reenter the dynamic phase when fed ad libitum. They predicted that unlesioned obese rats would not overeat subsequent to VMH lesions. With the use of insulin injections, they induced overeating and consequently, obesity in rats. The injections were terminated and the rats were lesioned bilaterally in the VMH. The obese rats did not become hyperphagic, but maintained their high body weight.

This "set point" hypothesis does not adequately explain the motivational weakness or finickiness in these rats. If anything, one would expect enhanced motivation during the dynamic phase. Furthermore, these rats do not "regulate" their body weight at an elevated level as do normals. Manipulations of diet palatability drastically alter their food intake and body weight (Carlisle & Stellar, 1969).

Grossman (1966) hypothesized that the alterations in feeding behavior in HYP hyperphagic rats is secondary to changes in affective reactions. VMH-lesioned rats have classically been described as hypersensitive to sensory stimulation. Due to this hypersensitivity, they are finicky (will not eat bad tasting food), and overeat very palatable foods. Using the same reasoning, their decreased work for food is an exaggerated emotional response. Grossman predicted that the decreased operant responding would not be specific to food reinforcement. He found that water-rewarded instrumental responses were also decreased in VMH-lesioned rats. He further tested his hypothesis by pharmacologically altering affective reactions. He found a decrease in operant responding for food reinforcement. The same pharmacological manipulations did not alter ad libitum feeding.

Additional research supporting this hypothesis demonstrated that HYP hyperphagic rats, given pre-lesion experience (for the purpose of habituating the affective response) with either quinine-adulterated water or instrumental responding for food, behaved more like normals than HYP-hyperphagic rats with no pre-lesion experience (Singh, 1973, 1974).

Although enhanced affective reactions may be part of the HYP hyperphagic syndrome, it is not the primary cause for the feeding disorder. If finickiness and reduced instrumental responding were a result of enhanced affective reactivity, which could be habituated over time, one would expect less of these responses during the static phase. During the static phase, the hyperphagic rats are more finicky (Franklin & Herberg, 1974; Sclafani, Springer & Kluge, 1976) and respond for food reinforcement at lower rates (Kent & Peters, 1973). It has also been demonstrated that the magnitude of the hyperphagia and the amount of finickiness can be independently varied depending upon the precise location of the lesion. Lesions that spare the most medial aspects of the VMH result in hyperphagia with minimal finickiness (Graff & Stellar, 1962). Furthermore, knife cuts in the area of the VMH produce hyperphagia without hyperreactivity (Sclafani, 1971).

Sclafani and Kluge (1974) have proposed a "dual lipostat model" for the control of hunger and appetite. According to this model, the HYP hyperphagia syndrome occurs because VMH damage increases appetite aroused by palatable foods, but does not directly alter hunger. Hunger, according to Sclafani and Kluge, is indirectly suppressed by the obesity. They propose two lipostatic mechanisms for the control of feeding. One mechanism maintains a lower body weight setpoint by controlling hunger drive.

Hunger is stimulated when the body weight falls below this lower setpoint. The other mechanism maintains an upper weight setpoint by controlling appetite. Appetite, which is stimulated by good tasting food, is inhibited when the body weight goes above the upper setpoint. According to this model, body weight should vary between the upper and lower levels according to food palatability. VMH lesions, according to Sclafani and Kluge, raise the upper appetite setpoint, without altering the lower setpoint. The static phase occurs when the animal reaches the upper setpoint level. The obesity reduces hunger drive because the body weight is well above the lower setpoint which stimulates the hunger drive.

In addition to the majority of the previous stated data, this model was based on the facts that (a) undeprived VMH-lesioned rats have a shorter latency to eat than normals when presented with "good" food, but a normal latency with less palatable foods or when both groups are food deprived (Sclafani, 1971), (b) HYP-hyperphagic rats that are food deprived from their pre-lesion weight bar-press for food at the same rates as deprived normals, while obese hyperphagic rats deprived from their elevated weight, bar-press less (Kent & Peters, 1973) and (c) under nondeprived conditions, dynamic hyperphagic rats bar-press more than controls for a palatable milk diet, while obese hyperphagic rats work at control levels (Sclafani & Kluge, 1974).

Sclafani & Kluge (1974) predicted from this model that obese rats fed an unpalatable diet would become hypophagic and lose weight only until they reach their lower setpoint level; they should then begin eating and maintain their weight at the same level as normal rats under the same conditions. Franklin and Herberg (1974) found that VMH-lesioned rats on a quinine adulterated diet defended their body weight at levels equivalent

to controls.

According to this model, little or no motivational deficits should occur in dynamic hyperphagic rats. There exists in the literature many controversial reports on this issue; however, the motivational deficit is certainly more pronounced during the static phase. Sclafani and Kluge believed that the lower "hunger" setpoint may be regulated by the LH, and when a motivational deficit occurs without obesity, there is probably damage to the LH feeding system.

Hypothalamic hyperphagia: neurophysiology. Numerous studies have been conducted using lesion and knife cut techniques in an attempt to clarify the neural circuitry involved in the regulation of satiety. Research utilizing knife cut techniques have been especially informative in localizing the crucial pathways because these manipulations primarily sever axons, while causing minimal destruction to cell bodies.

It has been found that knive cuts in the HYP which separate the VMH from the LH result in hyperphagia. Sclafani (1971) suggested that these cuts may be severing VMH inhibitory connections with the LH. Interestingly, he found that the further lateral these knife cuts were, the less hyperphagic and more finicky the rats became. This finding, which indicates that the hyperphagia and finickiness may have anatomically distinct origins, is consistent with earlier reports by Graff and Stellar (1962) that the most finicky rats had the medial portions of the HYP intact. It is also consistent with Sclafani's notion that motivational deficits resulting from VMH lesions are due to some LH destruction.

In a later study, Sclafani, Berner, and Maul (1975) utilized multiple knife cuts to determine the nature of the inhibitory influence of the VMH on the LH. They hypothesized that lateral cuts (which resulted in less

hyperphagia and more finickiness) severed both inhibitory and excitatory connections between the VMH and the LH, while more medial cuts (which result in greater hyperphagia with no finickiness) severed only the inhibitory connections. They predicted that medial cuts, in animals that previously had lateral cuts, should be ineffective because the LH and VMH were already separated. Conversely, lateral cuts should attenuate the hyperphagia by severing excitatory fibers in animals who previously had medial cuts. Contrary to their prediction, they found that medial cuts did increase the hyperphagia and obesity in rats previously given lateral cuts. This implies that many of the fibers severed, which produce hyperphagia, do not project directly to the LH.

HYP hyperphagia, which was generally produced in response to fairly large lesions in the VMH region, was believed to be the result of destruction to the VMH or afferent fibers from it. In careful neuroanatomical studies, Gold (1973) and others (Coscina, Godse & Stancer, 1976) found that lesions restricted to the VMH did not result in hyperphagia. Gold found that the most effective small lesions were rostral to the VMH. He noted that a group of NA fibers crossed midline in the area of his most effective lesions. According to Gold, these fibers (which are likely to be responsible for the hyperphagia) probably ascend from the ventral NA bundle (VNB).

Since that time, it has become evident that fibers ascending to the region of the VMH, rather than to discrete nuclei, are responsible for the hyperphagia. Gold (1970) found that bilateral parasagittal knife cuts alongside the paraventricular nucleus of the HYP (PVN) produce hyperphagia and obesity. In order to further delineate the area crucial to

the hyperphagia, Gold, Jones, Sawchenko and Kapatos (1977) utilized asymmetrical knife cuts. They reasoned that bilateral destruction in the system, even at different loci, should result in hyperphagia. A unilateral parasagittal HYP knife cut alongside the PVN was used in combination with contralateral, systematically manipulated coronal cuts. They found that when the coronal cuts were anterior to the PVN, no alterations in feeding occurred. When the coronal cut was caudal to the PVN, it resulted in hyperphagia and obesity. From this they concluded that the PVN is the rostral focus of a longitudinal satiety neurocircuitry.

Grossman (1971) reported that coronal knife cuts through the posterior HYP produced a marked hyperphagia and obesity. Since these cuts resulted in minimal cellular damage, it was suggested that their behavioral effects may be due to an interruption of fibers "en passage" from more posterior loci.

In an attempt to further elucidate the role of ascending pathways in the regulation of food and water intake, Grossman and Grossman (1977) examined the feeding and drinking behavior in rats following knife cuts to the tegmentum.

Knife cuts restricted to the central grey, or to the ventromedial portions of the tegmentum, resulted in no alterations in feeding behavior. They found, however, that more dorsal knife cuts within the tegmentum (just ventral to the central grey), frequently resulted in hyperphagia and hyperdipsia. Closer histological examination of these cuts indicated that the hyperphagia appeared to be associated with the cuts that extended furthest dorsal and lateral, while hyperdipsia was associated with more ventromedial cuts. They found in a subsequent group that

knife cuts that extended further lateral, which spared the medial areas cut in the previous group, frequently resulted in hyperphagia and never in hyperdipsia.

All of the knife cuts extended laterally to portions of the reticular formation, which is believed to contain components of the ascending NA pathways. The cuts that resulted in hyperphagia consistently involved a greater proportion of that region. They did not find, however, significant differences in forebrain NA depletion between the hyperphagic and non-hyperphagic rats.

The hyperphagia in these rats was not as large in magnitude as that resulting from VMH lesions. Furthermore, unlike HYP hyperphagic rats, these animals did not begin gaining weight immediately after the knife cuts. The hyperphagic animals lost unusually large amounts of body weight during the first 24 hours after surgery and had reduced body weights for up to 10 days. During days 11 and 20 post-surgery, however, the hyperphagic animals reliably gained more weight than controls.

Lesions in the midbrain tegmentum have also been reported to result in hyperphagia, although this syndrome is behaviorally distinct from HYP hyperphagia (Ahlskog, Randall & Hoebel, 1975). The magnitude of the hyperphagia is less, the diurnal cycle of feeding remains intact, and the rats are not finicky. Other indications that this syndrome is different is that unlike those following VMH-lesions, the behavioral effects of tegmental lesions are abolished by hypophysectomy (Ahlskog, Hoebel & Breish, 1974), and the effects of the two lesions appear to be additive.

Ahlskog (1974) reported the occurrence of this hyperphagia following electrolytic destruction of the VNB and following 6-hydroxy-dopamine (6-OH-DA) injections near this pathway. Catecholamine (CA) terminals are putatively selectively destroyed by 6-OH-DA. The chemical lesions resulted in almost total forebrain depletion of NA. DA was only slightly reduced while serotonin (5-HT) was unaltered. Pretreatment of 6-OH-DA injected rats with desmethylimipramine, a specified blocker of NA uptake, blocked the loss of NA, and prevented overeating. Animals which were injected with 6-OH-DA near the dorsal NA bundle (DNB) did not become hyperphagic. The results indicate that forebrain NA which ascends from some more caudal regions is inhibitory on feeding.

Although these behavioral effects are putatively due to the VNB destruction, it is unlikely that only the VNB was lesioned. The electrolytic lesions were likely to have destroyed several other pathways ascending through the midbrain. Furthermore, selective VNB lesions with 6-OH-DA could not possibly result in such drastic forebrain NA reductions.

Neurochemistry of Feeding

Chemical stimulation of the brain through cannulas has made it evident that NA plays a primary role in the HYP feeding system (Grossman, 1962a, 1962b). Much controversy exists, however, as to the precise relationship between NA and feeding. Both Leibowitz and Margules have demonstrated that important differences exist between alpha- and beta-adrenergic subsystems in the HYP.

Leibowitz (1970) suggests that there is an antagonistic relationship between an alpha-adrenergic "hunger" system (which elicits feeding) and

a beta-adrenergic "satiety" system (which suppresses feeding). She found that alpha-adrenergic agonists (NA and metaraminol) injected into the perifornical HYP elicited feeding in satiated rats, while injections of a beta-adrenergic agonist (isoproterenol) suppressed feeding in deprived rats. Epinephrine, which acts as both an alpha- and beta-adrenergic agonist elicited feeding at low doses (probably the alpha- effect) and inhibited feeding at higher doses (the beta- effect). The elicitation of the feeding response was blocked only by an alpha-adrenergic antagonist (phentolamine) while a beta- antagonist (propranolol), blocked the satiation response. Leibowitz also found that the beta-mediated satiety effects were potentiated by an alpha-antangonist. This, according to her model, should excite the beta- "satiety" system while blocking the alpha- "hunger" system.

Leibowitz (1976) found that while injections to the perifornical HYP resulted in both alpha- and beta- feeding effects, injections to more medial loci responded only to alpha-adrenergic injections. Conversely, more lateral injections responded only to beta- stimulation. Within the medial HYP, she found the PVN to be most sensitive to alpha-adrenergic stimulation. She hypothesized the existence of an alpha-adrenergic hunger system in the medial HYP and a beta-adrenergic satiety system in the LH which overlap in the perifornical area between them. This apparent contradiction with the lesion data (LH hunger center, VMH satiety center) is easily accounted for. She believes that both alpha- and beta- receptors are inhibitory in nature. She suggests that the beta- system suppresses food consumption by inhibiting the LH; while the alpha- effect results from inhibiting the medial HYP which disinhibits the LH.

Leibowitz (1976) has pointed out that there are similarities between NA induced and natural feeding. In both cases, there is drinking prior to eating and the amount of drinking is correlated with the amount of eating. She also finds that the feeding response can be elicited by very low doses of NA which she considers to be probable physiological levels.

Problems with Leibowitz's model, as an explanation of normal feeding, center on the facts that animals will not work to obtain food with chemical stimulation (Coons & Quartermain, 1970) and its inability to explain finickiness.

Margules has conducted a series of experiments in which he injected alpha- and beta-adrenergic agonists into the perifornical HYP and measured the intake of milk with varying sweetness. Some of his findings are similar to that of Leibowitz, while others are quite different.

Margules (1970a; 1970b) suggested that both alpha- and beta-adrenergic systems suppress feeding behavior. According to him, the alpha- system suppresses feeding through satiety, while the beta- system does so by taste aversions. In support of this, he found (unlike Leibowitz) that an alpha- agonist (NA) suppressed feeding. He also found that an alpha-blocker (phentolamine) produced feeding suppression (which Leibowitz found) only if the the milk was quinine-adulterated. With sweet milk, the rats overate in response to phenolamine.

The beta- agonist isoproterenol, Margules found, suppressed the intake of bitter milk, but not sweet milk. The beta- blocker resulted in intake of even bitter milk, although the actual volume was reduced.

Margules suggested that the inhibition of one system results in the enhancement of the other. Enhancing the alpha- system with either alpha-

agonists or beta- blockers reduced feeding regardless of tast. Activating the beta- system with either beta- agonists or alpha- blockers resulted in finickiness. He hypothesized that HYP hyperphagia is caused by a disruption of the alpha-satiety system which results in enhanced beta-taste responsivity.

A big advantage of Margules' model as compared to Leibowitz's is that it begins to explain the relationship between feeding, satiety and taste responsivity. There is, however, less empirical support of his data (there are very few reports of NA injections resulting in the suppression of feeding). He also uses in his studies higher doses of the drugs and has been unable to make any precise anatomical statements.

In an attempt to further explore the incongruous responses to NA injections reported by himself and Leibowitz, Margules (1972) manipulated the time of day of the injection. He found that NA injected in the dark part of a 12/12 L/D schedule (period of normally high feeding) reduced food intake while NA injections in the light enhanced feeding. Leibowitz (1976), however, was unable to replicate this finding.

Another line of research which may shed light on these discrepancies is that of Oomura, Ooyama, Tamamoto, Ono and Kobayashi (1969). They injected minute doses of NA into the HYP which were too small to elicit behavior. They found that in the LH, NA increased the activity of single units. In the region of the VMH, however, they found that NA increased some units and decreased others. This indicates the existence of two distinct NA sensitive systems that may be involved in feeding regulation. It is possible that both of these systems are alpha-adrenergic and may be differentially activated depending upon the dose, cannula location, time of day, diet or deprivation state.

Ritter and Epstein (1975) found that very low doses of NA injected into the HYP failed to elicit eating in satiated rats. These same doses, however, more than doubled the size of a meal if injected after the meal was initiated. They suggest that, under ad libitum feeding conditions, endogenous NA is released during a meal for the purpose of sustaining eating once it is initiated.

Since alterations in meal frequency suggest the operation of a control that initiates meals, or a hunger mechanism, and alterations of meal size suggest a terminating, or satiation mechanism, their data suggests that the release of endogenous NA during feeding increases food intake by an inhibition of satiety. In support of this hypothesis, Martin and Myers (1975) have found increased NA release in the vicinity of the PVN in animals during feeding, but not in satiated or food deprived rats that are not eating.

A further indication that the PVN is intimately involved in the regulation of feeding is that genetically obese rats were found to have significantly lower levels of NA in the PVN than controls (Cruce, Thoa, & Jacobowitz, 1976). This finding contradicts Ritter and Epstein's hypothesis since genetically obese rats have been reported to overeat by increasing their meal size (Becker & Grinker, 1977) and thus should have higher levels of NA.

Summary and Implications

The data discussed thus far indicate the existence of at least two, anatomically, neurochemically and functionally distinct neural mechanisms involved in the regulation of feeding behavior; a feeding

mechanism, and at least one (although probably more) satiety mechanism. As opposed to early suggestions that these mechanisms were controlled solely by feeding centers located in the HYP, recent data indicate that fibers that ascend to the HYP play a major role in their regulation. It is more likely that the HYP is the focal point of several food regulating systems in the brain. The lesion and knife cut data suggest that several separate, yet interconnected, pathways are involved in mediating food intake, satiety, and taste responsivity.

Although the implications of the data are not at all times consistent, there is an overwhelming amount of converging evidence indicating that the PVN plays a central role in the regulation of feeding behavior. Destruction of fibers passing either in or out of it have been found to be critical to the production of the HYP hyperphagia (Gold et al., 1977), it is the most sensitive locus to NA induced feeding (Leibowitz, 1976), and genetically obese rats have decreased NA in that nucleus (Cruce et al., 1976).

The function of the PVN in the regulation of feeding behavior is believed to be inhibitory. Although the precise role is not known, the data indicate that it is involved in the regulation of satiety, rather than hunger. Support for this is (a) animals will not work to obtain food during NA stimulation to the PVN (Coons & Quartermain, 1970), (b) NA release in the PVN occurs during meals rather than prior to their onset (Martin & Myers, 1975), (c) genetically obese rats that overeat by increasing meal size (Becker & Grinker, 1977) have decreased levels of NA in the PVN (Cruce et al., 1976).

The data also indicate that the role of the PVN in the regulation

of satiety is NA mediated (Leibowitz, 1976). HYP NA innervation ascends almost entirely from nuclei in the hindbrain (Ungerstedt, 1971). It is therefore likely that destruction of the NA nuclei or pathways crucial to PVN innervation, should result in alterations in feeding behavior.

Destruction of the VNB, which is the major NA pathway innervating the HYP, has been found to result in hyperphagia and obesity. Although these lesions significantly reduce HYP NA levels, the amount of depletion does not correlate with the magnitude of the hyperphagia. VNB lesions produced using 6-OH-DA, which result in greater reduction of NA than electrolytic lesions, do not produce a more pronounced hyperphagia (Ahlskog, 1974; Grossman & Grossman, 1977).

Destruction of the DNB, the other major NA pathway ascending from the hindbrain, results in no changes in feeding behavior (Ahlskog, 1974).

If one assumes that NA is the neurotransmitter mediating the hyperphagic behavior, yet NA depletions within the HYP are not correlated with the magnitude of the hyperphagia, then it is likely that the NA mediating the behavior is not from a major source of HYP NA, but rather from an innervation of a smaller magnitude, to discrete nuclei. Thus, alterations in feeding behavior resulting from NA depletions within these specific nuclei, would minimally alter the NA levels of the entire HYP. Furthermore, if the pathway by which this NA innervation ascends to the HYP is anatomically close to the more prominent NA pathways (the VNB or the DNB), it would be difficult to sever it without causing damage to the larger pathway. Therefore,

destruction to this pathway is likely to result in a large NA depletion, but the magnitude of the depletion would not be correlated with the magnitude of the hyperphagia.

According to this model, a pathway that meets the following criteria may be responsible for mediating at least some aspects of HYP hyperphagia.

1. it must ascend from NA nuclei.

2. destruction of the pathway must result in small depletions of NA to the HYP as a whole.

3. destruction of this pathway must result in highly significant depletions of NA to specific HYP nuclei; in particular, the PVN.

4. it must ascend through the midbrain in close proximity to one of the more prominent NA pathways.

I suggest, that a pathway meeting these requirements ascends from the area of either the principal LC or the subcoeruleus.

The Locus Coeruleus and Subcoeruleus

The nucleus locus coeruleus (LC) in the rat is a small (1.0 mm rostral-caudal; 0.4 mm medial-lateral; 0.6 mm dorsal-ventral), but dense group of NA cell bodies which is located in the dorsolateral pons, in the floor of the fourth ventrical, lateral to the dorsolateral tegmental nucleus and medial to the nucleus of the trigeminal motor nerve (Cedarbaum & Aghajanian, 1978).

A variety of techniques have demonstrated that the cells of the LC project axons, and are a major source of NA, throughout the CNS. Caudal projections of the LC supply NA input to various loci in the

medulla and spinal cord; other projections have been found to innervate the cerebellum (Lindvall & Bjorklund, 1974; Nygren & Olson, 1977; Olson & Fuxe, 1971; Ungerstedt, 1971).

In recent years a large number of studies have investigated the ascending projections of the LC. Early histofluorescence studies (Dahlstrom & Fuxe, 1964; Ungerstedt, 1971) indicated that the source of midbrain and forebrain NA was either of two ascending NA pathways; the DNB or the VNB. The DNB, which ascends through the midbrain and LH, was believed to innervate primarily the ipsilateral hippocampus and neocortex. The source of this bundle is the LC. The VNB, which was believed primarily to innervate the HYP, ascends from what Dahlstrom and Fuxe (1964) labeled cell groups A_1, A_2, A_5, and A_7. Due to the limited sensitivity of these histofluorescence techniques, the presence of other, less prominent, ascending NA pathways and terminals could not be adequately assessed.

The subcoeruleus is a more diffuse group of large NA cell bodies which is located primarily ventrolateral to the principal LC. Dahlstrom and Fuxe (1964) defined the subcoeruleus as the ventral part of the LC (cell group A_6), A_7, and the NA cell bodies between these two groups.

Olson and Fuxe (1972) reported that subsequent to knife cuts which separated the subcoeruleus from the forebrain, fluorescence of NA terminals dissappeared in the PVN and the dorsomedial HYP nucleus. From this data they suggested that the VNB has two parts; one arising from the medulla (primarily A_5) and the other from the subcoeruleus. This subcoeruleus-HYP pathway corresponds to a distinct "intermediate

bundle" reported by Maeda and Shimizu (1972). According to Olson and Fuxe, however, this projection rapidly joins the one arising from the medulla to form the VNB. They also found that knifecuts in the midbrain, that transected only the DNB, resulted in a disappearance of NA nerve terminals in only the cortex and thalamus.

More recently, using glyoxylic acid histofluorescence, Lindvall and Bjorklund (1974) mapped out, in detail, the organization of the ascending catecholamine systems in the rat brain. With this more sensitive histofluorescence technique they revealed smaller and more diffuse NA pathways. They confirmed earlier reports that the major rostral projection of the LC is through the DNB to the telecephalon, but also found that the LC and subcoeruleus project rostrally through the "central tegmental tract" and the "periventricular pathway," both of which contribute inputs to various parts of the HYP.

Biochemical (punch) techniques, which are more sensitive than histofluorescence, have demonstrated NA innervation of specific HYP loci from the LC. These techniques involve lesioning the LC and measuring NA levels in discrete nuclei. Using this technique, Kobayashi, Palkovits, Jacobowitz and Kopin (1975) confirmed the telencephalic innervation by the LC previously found using histofluorescence. They also found significant depletions of NA in the PVN and the periventricular nucleus (PER) of the ipsilateral HYP. The NA reductions in these loci were 39 percent and 43 percent respectively, indicating that the NA innervation is not solely from the LC. Jones, Halaris, McIlhany, and Moore (1977a) also found significant depletions of NA in the ipsilateral HYP following LC lesions.

Dopamine-beta-hydroxylase (DBH) is the enzyme that catalyzes the conversion of DA to NA. It is a specific marker of NA neurons and its activity is known to parallel the anterograde degeneration of NA fibers (Reiss & Molinoff, 1972). Ross and Reiss (1974) measured DBH activity in various parts of the CNS following LC lesions and found significant decreases in the spinal cord, telencephalon, and hypothalamus. The percentage decrease of DBH activity was similar to the reductions in NA reported by Jones et al. (1977a) and Kobayashi et al. (1975).

A recent series of studies have again confirmed the existence of LC-HYP connections in the rat. Using axonal transport techniques, Jones et al. (1977a) found significant amounts of radioactivity in the ipsilateral HYP of rats 24 hours after unilateral injections of labeled protein into the LC. Using autoradiography (Jones & Moore, 1977b) they found axonal projections from the LC in the PER, the supraoptic nucleus, and the PVN of the ipsilateral HYP.

The histofluorescence, biochemical, and neuroanatomical data reviewed indicate that although HYP NA innervation does not come primarily from the LC area, major inputs to at least some HYP nuclei arise from either the principal LC, the subcoeruleus, or both. The fact that several investigators (Dahlstrom & Fuxe, 1964; Pickel, Segal, & Bloom, 1974; Ungerstedt, 1971) have been unable to detect evidence of LC-HYP connections further indicates that it is not a major source of innervation to the area.

Since destruction of the DNB, which is the major pathway ascending from the LC, does not decrease fluorescence in the HYP (Olson &

Fuxe, 1972; Ungerstedt, 1971), it is unlikely to be the pathway connecting the two area. LC lesions, therefore, denervate ascending pathways other than the DNB. Consequently, DNB lesions should not effect HYP functioning, or behavior, in ways identical to LC lesions.

Finally, those studies that found relationships between the LC (or subcoeruleus) and specific nuclei within the HYP, all indicated that a pathway ascending from the LC (which is unlikely to be the DNB) has terminals in the PVN.

Hypothesis

The data indicate that feeding behavior is regulated by several separate, yet interrelated, neural circuits, rather than by feeding and satiety centers located solely in the HYP. Although HYP loci may be the focal point of these regulatory mechanisms, fibers ascending from more caudal regions appear to be critical to the maintenance of the system. Neurophysiological and neurochemical data suggest, that within the HYP, the PVN is of primary importance in the regulation of feeding.

Neurochemical manipulations of the PVN demonstrate that NA plays a major role in the control of food intake (Cruce et al., 1976; Leibowitz, 1976; Martin & Myers, 1975). From lesion data, however, this is not as apparent. Lesions that destroy the VNB result in HYP NA depletions and hyperphagia, but the magnitude of the hyperphagia is not correlated with the amount of NA depletion. Lesions produced using 6-OH-DA result in greater NA depletions, but not more hyperphagia (Ahlskog, 1974; Grossman & Grossman, 1977).

It is possible that NA depletion to the entire HYP is not a prerequisite for hyperphagia, but rather depletions in one or more specific nuclei. If depletions occurred exclusively in these nuclei, minimal reductions would be measured in the HYP as a whole. If a distinct fiber tract which was in close proximity to a more prominent pathway (the VNB) was responsible for NA innervation to these nuclei, it would be difficult to sever it without causing destruction to the larger pathway. Therefore, lesions resulting in hyperphagia would also result in large HYP NA depletions. These depletions, however, would be correlated with the extent of destruction to the larger pathway, and not the magnitude of the hyperphagia.

Four criteria were stated that must be met, according to this model, before a fiber tract is to be considered the innervating pathway critical to the hyperphagia. The intermediate bundle described by Maeda and Shimizu (1972) meets all these criteria. It ascends from the NA rich LC and/or subcoeruleus; it is not a primary source of NA to the HYP; it has many terminals in the PVN; and it ascends to the HYP in close proximity to the VNB.

This model predicts that (a) the magnitude of the hyperphagia resulting from lesions and knife cuts posterior to the HYP should be proportional to the NA depletion in the PVN, and (b) destruction of the intermediate bundle that leaves the VNB intact, should result in hyperphagia.

These experiments were designed to test the second prediction made from this model. Because transecting the fibers of the intermediate bundle without disrupting the VNB is technically unfeasible,

the pathway was disrupted at its source, in the dorsal brainstem. At this level, it is more isolated from the VNB although in closer proximity to the DNB. Alterations in feeding behavior that do occur, however, are unlikely to be due to DNB disruption.

A variety of measures of feeding behavior were recorded in the lesioned rats. These measures included food intake, body weight, meal pattern analyses and response to quinine adulteration. If one assumes that the classical HYP hyperphagia syndrome is due to a disruption of several neural circuits regulating feeding behavior, it is unlikely that these hindbrain lesions will result in equivalent behaviors on all the measures.

If the predicted hyperphagia is due to PVN denervation, these lesions should not result in hyperphagia until several days after the lesion when complete degeneration occurs down the axon (Ross & Reiss, 1974).

It is also unlikely that these animals will become finicky. Diverse data indicate that the finickiness associated with HYP hyperphagia may be due to a separate mechanism. Behavioral data indicate that it may be due to the obesity rather than specific lesion effects (Franklin & Herberg, 1974; Sclafani et al., 1976). According to this, they will become finicky if they become obese. Neurophysiologial (Graff & Steller, 1962; Sclafani, 1971) and neurochemical (Margules, 1970a; 1970b) data indicate, however, that the hyperphagia and elevated taste responsivity are due to distinct neural systems. It is doubtful that these hindbrain lesions would impinge on both neural circuits.

EXPERIMENT 1

Rationale

This experiment examined the effects of bilateral LC lesions on feeding behavior. Throughout the experiment the subjects were maintained on a sweetened milk diet rather than pellets in order to maximize the probability of observing alterations in feeding. If the lesions result in high taste responsivity along with hyperphagia the overeating will be increased while with the dry pellets, the hyperphagia may not be apparent.

It was also believed that meal patterns resulting from a calorically dense milk diet are more readily interpreted. Data has indicated that on a solid food diet, hyperphagic rats overeat by consuming more meals, which would indicate increased hunger. This increase in meal frequency, however, is due to the bulk of the dry food. If the stomachs of these animals are surgically enlarged, they eat larger meals (which reflects a satiety deficit), as they do with milk diets (Teitelbaum & Campbell, 1958).

Another advantage of using a milk diet is the availability of two measures of feeding behavior; milk intake and number of licks on the milk tube. Differential changes in these two measures will reflect changes in feeding efficiency. An increase in the number of licks without a corresponding change in milk intake would indicate decreased feeding efficiency. This change is likely to indicate either somatosensory or motor debilitation. In either case, it would reflect an increased energy expenditure for the acquisition of food.

Increases in feeding behavior with this diet may reflect either

a true hyperphagia or an increased taste responsivity to the sweetened milk. In order to distinguish between these two possibilities, the milk was adulterated with quinine for four consecutive days. The rats that overeat in response to the taste of the sweetened milk should show large reductions in feeding in response to quinine adulteration as compared to controls. A non-taste responsive hyperphagic rat should show reductions in feeding equivalent to controls.

During quinine adulteration, only measures of actual milk intake were recorded. Pilot data has indicated that during quinine adulteration large amounts of spillage occur (which is accounted for in the milk intake measure) and the lick data does not accurately reflect food consumption.

Although controversy exists (Amaral & Routtenberg, 1975; van der Kooy & Phillips, 1977), there is evidence indicating that electrodes aimed at the dorsal brainstem that elicit ICSS, are likely to be in the area of the LC (Crow, Spear, & Arbuthnott, 1972; Ellman, Ackermann, Farber, & Steiner, 1973; Sinnamon, Shaw, Amaral & Woodward, 1978). The subjects were therefore, chronically implanted, and screened for ICSS to maximize the probability of the lesions being in the LC.

Another advantage of chronically implanting the subjects prior to the experiment is the decreased trauma of the lesions. Rather than heavily anesthetizing the subjects and performing surgery and lesions together, the rats were lightly anesthetized and the entire lesion procedure took only a few minutes.

Three types of controls were used in the experiment: (a) chronically implanted rats with lesions in brainstem loci lateral to the

pontine central grey, (b) lesions in chronically implanted rats that were intended to be in the LC but missed, and (c) non-lesioned controls.

Method

Subjects

The subjects were 12 female, Sprague-Dawley, albino rats weighing approximately 300g at the start of the experiment. All subjects were housed individually under 12 hours of light (0800-2000) and 12 hours of dark (2000-0800) lighting conditions throughout the experiment and had free access to Teklad mouse pellets and water.

Surgery

Rats were anesthetized with Sodium Thiopental (45 mg/kg) and chronically implanted with two bipolar, stainless steel electrodes (Plastic Products). The electrodes were 0.5 mm at their widest extent and insulated except at the tips. The electrodes were aimed bilaterally at the pontine dorsal brainstem (DBS) (with the use of a Kopf stereotaxic instrument) either in the area of, or lateral to, the LC. The electrodes directed toward the area of the LC (n=15) were implanted at a 16° angle to the mid-sagittal plane, 1.5-2.0 mm posterior to the lambda suture, 3.0 mm to the left and right of a line extrapolated from the sagittal suture and 7.1-7.3 mm below the surface of the skull. The incisor bar was set at -5 mm. The electrodes aimed lateral to the LC (n=2) were implanted using the same coordinates, but at a 0° angle to the mid-sagittal plane and 7.0 mm below the surface of the skull.

Sham surgery (n=2) included anesthetising the rat, placing it in

the stereotaxic instrument, and drilling holes in the skull. The dura was not punctured.

Screening Procedure

After a recovery period ranging from one to two weeks, the chronically implanted animals were screened for ICSS at each electrode site. They were shaped in an operant conditioning chamber to bar press on a continuous reinforcement schedule for 0.25 second trains of 60 Hz sinusoidal stimulation. Screening intensities ranged from a minimum of 10 μa to a maximum of 145 μa. This range encompasses the intensities that have been found to elicit ICSS in rats. Shaping in all subjects began at 10 μa. If ICSS behavior did not occur, the intensity of the stimulation was gradually increased until either the stimulation appeared (subjectively) aversive to the animal or the maximum intensity was reached. Screening sessions had a duration of 30 minutes per electrode site. No electrode was screened for ICSS more than five times. Rats with electrodes aimed at the LC that responded at a rate greater than 50 presses in five minutes at each electrode site, and rats with lateral implants which did not self-stimulate at either electrode site, were used in the experiment. No rats were used that self-stimulated from only one electrode site. Eight out of the 15 rats with electrodes directed toward the LC and both rats with lateral implants met this criterion.

Lesions

Rats were anesthetized with Sodium Thiopental (30 mg/kg). Bilateral radio frequency lesions were produced by passing a one to eight mA current from the electrode tips to a metal plate (which

served as an indifferent) in contact with the animals' ventral surface for 30 seconds. These parameters have been found to produce hindbrain lesions which alter behavioral responses elicited by stimulation to the HYP (Farber et al., 1976).

Diet

At the onset of the experiment food pellets were replaced by a sweetened milk diet similar to that described by Sclafani and Berner (1976). It consisted of 300 ml of Borden's Magnolia Milk, 600 ml water, 0.3 ml poly-visol vitamins (Mead Johnson), and three drops of 10% formalin. At the end of the experiment a quinine-adulterated diet was used. It was the same as the milk diet except for the addition of 270 mg of quinine sulfate (0.3% solution). Water was available at all times.

Feeding Apparatus

Each rat was maintained in a 16" x 9" x 8" plexiglass chamber. Calibrated milk bottles (in ml) were suspended so that the sipper tube was approximately 0.5 cm outside of a 1.4 cm diameter hole in the wall of the rats' chambers. This method, similar to that described by Kissileff (1969), minimizes random contact with the sipper tube and prevents continuous contact with the tube during feeding. A calibrated cup below the sipper tube was used to collect spillage. The total amount of spillage, which was recorded in ml at the end of each 12-hour lighting period, was subtracted from the reduction of the milk level in the bottle during that period. The sipper tube and floor grid of the chamber were wired to a drinkometer (Scientific Prototype Mfg. Corp., Model 101k) so that each lick produced an individual electrical pulse.

Recording and Scoring Procedure

During seven days of baseline (BL) and 21 post-lesion (PL) days each lick was counted on both manual counters (separate counters for the light and dark periods) and cumulative recorders calibrated at 100 counts per inch with a paper speed of 12 inches per hour.

The temporal distribution of licks recorded on the cumulative recorders were scored for meal size (number of licks per meal) and meal frequency. A meal was defined as no less than ten licks separated by at least ten minutes from any other licks. Licks that occurred outside of meals were counted and recorded as non-meal licks.

Histology

At the end of the experiment the rats were decapitated and the brains removed. The hindbrain was separated from the remainder of the brain and placed in 10% formalin. After a minimum of 24 hours the hindbrain was put into a 30% sucrose solution (in 10% formalin) for a minimum of 72 hours. The brains were then frozen and cut into 40 micron coronal sections. The sections were stained with luxol fast blue and cresyl violet according to the method of Kluver and Barrera (1953). Localization and extent of lesions were determined by a judge who had no knowledge of the behavioral data. The magnitude of destruction to the LC, the dorsal tegmental nucleus (DTN), the trigeminal motor nucleus (TMN), and the subcoeruleus were determined.

Protocol

Chronically implanted and sham operated rats were housed in the feeding chambers and maintained permanently on the milk diet. After 15 to 20 days of adaptation to the new milk diet (depending

upon the availability of equipment) seven days of BL feeding were recorded. Bilateral radio frequency lesions were then placed in the DBS of the chronically implanted rats. The shams were anesthetized. Twenty-one days of ad libitum PL feeding data were recorded for each rat. Subsequent to this, response to four days of quinine adulterated milk was measured by weight loss and change in food intake in nine of the rats (seven LC and two lateral implants). The animals were then sacrificed and histology was performed.

Each day at five and one half hours after the onset of the light period, animals were weighed, their cages were serviced, and they were given fresh milk.

The data was analyzed using a profile analysis (Morrison, 1976). This analysis was used because of its ability to make several within and between-group comparisons. With the use of a Hotelling-Lawley trace it also compares, between groups, the trends of behavioral changes over time. These analyses were performed on changes in milk intake, total number of licks, body weight, number and size of meals, light-dark distribution of feeding, and response to quinine adulteration. The amount of destruction to specific nuclei were correlated with the magnitude of changes in feeding behavior.

Results

Histology

Six of the 12 rats had bilateral destruction involving the LC. The six non-LC-lesioned rats consisted of two with lesions far lateral to the LC (FL), two with lesions anterior and ventral to the LC (A-V), and two shams.

The lesions in the LC group extended to other structures besides the LC. Most of them impinged upon or destroyed many adjacent structures including the DTN, the TMN and the subcoeruleus. Some LC lesions extended as far lateral as the brachium conjunctivum and as ventral as the medial longitudinal fasciculus (MLF). Figure 1 shows the extent of the bilateral LC lesions in one animal. The left lesion in this figure is one of the largest in the group, whereas the right is among the smallest.

Figure 2 is representative of the FL lesions. These lesions caused destruction to parts of the medial cerebellar peduncles, the trochlear nerve, and the trigeminal spinal tract. The entire pontine central gray was left intact in animals with FL lesions.

Figure 3 shows an example of an A-V lesion. These lesions caused destruction to the superior cerebellar peduncles and destroyed or extended ventral to the MLF.

Figure 4 shows the maximal extent of all the lesions for all the groups. There is little or no overlap between the lesions of the different groups within the pontine tegmentum. There is, however, much overlap between the LC and A-V groups at, and anterior to, the ponto-mesencephalic junction.

Data Analysis

Due to equipment failure, the lick data was lost for one sham animal. All analyses using that data (e.g., meal pattern analyses) will be based upon 11 subjects. As shown in appendix A, there were no significant differences between the three types of non-LC-lesioned rats on all measures of feeding behavior tested except for body

weight. Therefore, those groups were combined to form the control group for all subsequent analyses except body weight. Appendix B contains for each group the mean changes from BL during each week post-lesion for all the measures that the analyses were performed upon.

Overall feeding behavior. During the first week post-lesion (PL1) the LC group showed no significant change in milk intake (measured in ml) as compared to controls ($F=1.95$, $df=1,10$, $p>.10$). The LC group reduced their feeding to 92.6% of baseline (BL) levels while controls reduced their milk intake to 81.3% (see figure 5). Feeding behavior, as measured by the total number of licks, did differ significantly between the groups ($F=8.92$, $df=1,9$, $p<.05$). During this time the controls decreased their mean number of licks to 80.3% of BL levels while the LC group had a 7.2% increase (see figure 6).

During the second week post-lesion (PL2) the LC group significantly increased its feeding, compared to controls, as measured by milk intake ($F=8.51$, $df=1,10$, $p<.05$) and number of licks ($F=10.39$, $df=1,9$, $p<.05$). The mean milk intake of the LC-lesioned rats was 19.0% above BL while the mean number of licks was 40.8% over BL. The mean milk intake and number of licks for the control animals were 98.6% and 96.1% of BL respectively (see figures 5 & 6).

During post-lesion week three (PL3) the LC-lesioned rats further increased their feeding compared to controls as measured by milk intake ($F=36.06$, $df=1,10$, $p<.0001$) and number of licks ($F=16.71$, $df=1,9$, $p<.005$). The mean milk intake during PL3 was 34.2% above BL for the LC group and 4.3% below BL for the controls (see figure 5). The LC

group increased their mean number of licks by 49.9% while the controls had an 11.2% reduction (see figure 6).

The Hotelling-Lawley trace indicated significant differences in the trends over time between the groups for both milk intake ($F=11.04$, $df=3,8$, $p<.005$) and number of licks ($F=5.65$, $df=3,7$, $p<.05$). Within the LC-lesioned rats, no significant changes in milk intake ($F=0.60$, $df=1,5$, $p>.10$) or number of licks ($F=0.81$, $df=1,5$, $p>.10$) occurred between BL and PL1. From PL1 to PL2, however, both milk intake ($F=18.34$, $df=1,5$, $p<.01$) and number of licks ($F=29.14$, $df=1,5$, $p<.005$) significantly increased. The LC lesioned rats further increased their milk consumption during PL3 ($F=7.32$, $df-1,5$, $p<.05$) but not their number of licks ($F=0.66$, $df=1,5$, $p>.10$) (see figures 5 and 6).

Body Weight. Since significant differences were found between the three types of non-LC-lesioned rats, they were not grouped for these analyses. Significant differences in the change of body weight from BL were found between the four groups at the end of PL1 ($F=5.06$, $df=3,8$, $p<.05$) and PL2 ($F=6.05$, $df=3,8$, $p<.05$), and were just short of significance at the end of PL3 ($F=3.52$, $df=3,8$, $p>.10$).

No significant differences were found in the changes in body weight during PL1, PL2, or PL3 between the LC-lesioned group and the FL group ($F=1.70$, $df=1,6$, $p>.10$; $F=5.50$, $df=1,6$, $p>.05$; $F=0.00$, $df=1,6$, $p>.10$) or the sham operated group ($F=0.15$, $df=1,6$, $p>.10$; $F=0.66$, $df=1.6$, $p>.10$; $F=0.43$, $df=1,6$, $p>.10$). The A-V group, however, gained significantly more weight from BL than the LC lesioned rats during PL1 ($F=11.41$, $df=1,6$, $p<.05$), PL2 ($F=16.80$, $df=1,6$, $p<.01$) and PL3 ($F=6.43$, $df=1,6$, $p<.05$).

Within the LC lesioned group, no significant changes in body weight occurred between the last day of BL and the last day of PL1 ($F=2.44$, $df=1,5$, $p>.10$) or between the last day of PL1 and the last day of PL2 ($F=0.31$, $df=1,5$, $p>.10$). At the end of PL3, however, the LC lesioned rats weighed significantly more than they did at the end of PL2 ($F=9.35$, $df=1,5$, $p<.05$). Figure 7 shows the mean body weight for LC-lesioned and non-LC-lesioned rats on the last day of BL, PL1, PL2, and PL3.

Meal Patterns. Throughout the experiment, more than 99% of all daily licks occurred during meals in both groups. Because of this, no analyses were performed on non-meal licks. During BL the mean number of daily meals for all subjects was 9.2. The mean meal size was 1422 licks.

The hyperphagia in the LC-lesioned group was characterized by an increase in the number of meals, while meal size remained unaltered. The increase in number of meals for the LC group as compared to controls was significant during PL1 ($F=5.72$, $df=1,9$, $p<.05$) and PL2 ($F=6.61$, $df=1,9$, $p<.05$), and was just short of statistical significance during PL3 ($F=4.50$, $df=1,9$, $p<.07$). No significant difference occurred in the meal frequency trends between the groups over time ($F=2.53$, $df=3,7$, $p>.10$).

The LC lesioned rats significantly increased their meal frequency from BL to PL1 ($F=40.22$, $df=1,5$, $p<.005$). No significant changes occurred, however, between PL1 and PL2 ($F=0.02$, $df=1,5$, $p>.10$) or PL2 and PL3 ($F=0.00$, $df=1,5$, $p>.10$) (see figure 8).

As shown in figure 9, the mean change in meal size between the

groups was insignificant during PL1 ($F=1.30$, $df=1,9$, $p>.10$), PL2 ($F=2.14$, $df=1,9$, $p>.10$) and PL3 ($F=0.18$, $df=1,9$, $p>.10$). No differences occurred between the groups in changes in meal size over time ($F=1.54$, $df=3,7$, $p>.10$). Within the LC group, however, there was a significant reduction in meal size from BL to PL1 ($F=16.27$, $df=1,5$, $p<.01$) followed by gradual increases which fell just short of significance between PL1 and PL2 ($F=4.85$, $df=1,5$, $p<.10$) and was insignificant between PL2 and PL3 ($F=0.05$, $df=1,5$, $p<.10$).

Light/Dark Feeding. Increases were observed in the hyperphagic rats (PL3) during both light and dark parts of the cycle. As shown in Table 1, there were no changes in the proportion of feeding during either lighting period as measured by milk intake ($F=0.06$, $df=1,10$, $p>.10$) or number of licks ($F=0.00$, $df=1,9$, $p>.10$). Throughout the experiment, all rats did approximately 70% of their feeding during the dark period. No significant differences occurred between the groups in the trends of the light-dark proportion of feeding for either milk intake ($F=0.53$, $df=3,8$, $p>.10$) or number of licks ($F=0.15$, $df=3,7$, $p>.10$).

Quinine Adulteration. The milk intake of the two groups was not differentially reduced as compared to prequinine levels during quinine days one ($F=1.45$, $df=1,8$, $p>.10$), two ($F=0.89$, $df=1,8$, $p>.10$), three ($F=0.01$, $df=8$, $p>.10$) or four ($F=3.78$, $df=1,8$, $p>.05$). No significant differences occurred between the groups in the changes in feeding over time in response to quinine adulteration ($F=1.02$, $df=4,5$, $p>.10$). All animals significantly reduced their feeding in response to quinine adulteration during the first day of quinine ($F=26.45$, $df=1,9$, $p<.0001$). This was followed by a gradual return to BL feeding levels by quinine day four (see figure 10).

Lesion-feeding Correlations. Pearson correlation coefficients were calculated to determine the relationships between changes in feeding behavior and the percent destruction to the LC, DTN, TMN, and subcoeruleus. The changes in feeding behavior were measured by percent of BL milk intake and number of licks (see Table 2). The magnitude of destruction to all the structures except the DTN significantly correlated with the changes in milk intake. The highest correlation was with subcoeruleus destruction ($r=.79$, $p=.007$).

The change in number of licks correlated significantly with the magnitude of destruction to all the structures except the subcoeruleus ($r=.49$, $p>.10$). Destruction of the TMN correlated highest with changes in number of licks ($r=.85$, $p=0.002$).

Discussion

As predicted, the LC lesioned group became hyperphagic. This increase in feeding, however, was quite different than that following VMH lesions.

The animals did not begin overeating immediately after the lesions as do HYP hyperphagic rats. This is consistent with the finding that it takes approximately seven days before significant reductions of DBH occur in the HYP following LC lesions (Ross & Reis, 1974).

Another major difference is that the LC-lesioned rats did not get obese. During the first two weeks post-lesion, the hyperphagic rats gained weight at slower rates than controls. It was not until PL3 that the hyperphagic rats began gaining weight more rapidly. This body weight data is similar to that reported by Grossman and

Grossman (1977) following knife cuts in the rostral brainstem. They found that for 10 days following the knife cuts, hyperphagic rats gained weight at slower rates than controls. They suggested that the slow rise in body weight may be due to increased energy loss which compensated for the hyperphagia. This data indicates that the number of licks increased more rapidly than the milk intake indicating increased energy expenditure during feeding.

The meal pattern analysis did not reveal increased meal size in the hyperphagic rats as is commonly found with HYP hyperphagia. These animals increased their meal frequency which indicates that the enhanced feeding may not be due to a satiety deficit, but rather increased hunger.

The hyperphagia was not due to increased taste responsivity in conjunction with the palatable diet. This is demonstrated by the fact that their food reductions in response to quinine adulteration were equivalent to controls.

Some data has indicated that LC lesions may result in hyperdipsia (Osumi, Oiski, Fujiwara, & Takaori, 1975). If this is true, the increased milk consumption may have been due to hyperdipsia rather than hyperphagia. The rats, although allowed free access to water, drank primarily milk.

The lesions in this experiment were quite large. Although the animals were grouped based upon LC destruction, most of the hyperphagic rats also had destruction to the TMN, the DTN, and several more ventral loci. Because of this, it is impossible to make a precise anatomical statement about the area causing the hyperphagia,

although, correlational data indicate that destruction to the sub-coeruleus best predicts the magnitude of the hyperphagia (defined as milk intake). TMN destruction best predicts enhanced licking which is probably related to motor deficits.

Prior to proceeding with the second experiment, the histology was carefully analyzed. An area was selected that best represented the bilaterally destroyed loci in the hyperphagic rats which was intact at least unilaterally in all of the lesioned controls. Figure 11 represents that area which will be referred to as the ventral LC (VLC). The VLC extends medial, lateral and ventral to the principal LC, but does not include the dorsal portion of the nucleus. This data indicates that destruction of some loci within the VLC is responsible for the hyperphagia.

EXPERIMENT 2

Rationale

This experiment was designed to further explore the role of the VLC in the regulation of feeding behavior. Throughout this experiment, animals had free access to 45 mg standard formula Noyes pellets and water. The pellets were available on a fixed interval-five second schedule of reinforcement. This schedule was found to be effective in preventing the rats from hoarding the food, therefore, allowing the measurement of the temporal pattern of feeding. Both food and water intake were recorded.

In order to make a more precise anatomical statement, approximately half of the rats were lesioned without prior chronic implantation of electrodes. Lesions produced in this manner are generally smaller than those produced from chronically implanted electrodes.

The meal pattern data in the first experiment indicated that the hyperphagic rats may have been hungrier than controls. In this experiment that possibility was further explored through the use of meal pattern data, quinine adulterated pellets, and a modified progressive ratio task to measure motivation.

To test whether the hyperphagia is due to destruction of the principal LC and/or its projections to the cortex, this experiment examined changes in cortical NA levels following the lesions. The rats were grouped as either bilateral VLC destruction or control.

Method

Subjects

The subjects were 22 female, Sprague-Dawley, albino rats weigh-

ing approximately 330g at the start of the experiment. All subjects were housed individually under 12 hours of light and 12 hours of dark lighting conditions throughout the experiment and had free access to Teklad mouse pellets and water.

Surgery

The surgical procedures were the same as those used in Experiment 1 for the implantation of electrodes in the DBS in the area of the LC and for sham surgery.

Screening

The screening procedure for the chronically implanted rats was identical to that used in Experiment 1. Rats that responded at a rate greater than 50 presses in five minutes at each electrode site were used. Ten out of 13 chronically implanted rats met this criterion.

Lesions

Chronically implanted subjects. These rats were lesioned according to the procedure described in Experiment 1.

Non-chronically implanted subjects. Rats underwent the procedure described for the chronic implantation of electrodes aimed at the LC. After the electrodes were lowered into position, they were connected to the lesion maker (Grass Inst. Co., Model LM4). Bilateral lesions were produced using the parameters described. The electrodes were then removed instead of being chronically affixed as in the surgical procedure.

Diet and Feeding Apparatus

The animals were housed in 16" x 9" x 8" plexiglass chambers. The chamber had a food tray and lever mounted on one wall. A lever

press closed a contact that activated a feeder on a fixed interval-five second schedule of reinforcement. Each reinforcement was comprised of a 45 mg standard formula Noyes pellet. Water and access to the lever were available ad libitum.

The quinine adulterated diet consisted of the same size and formula pellets adulterated with 0.12% quinine by weight.

Recording and Scoring

Food-reinforced lever presses were counted independently for the light and dark periods. The temporal distribution of these presses throughout the day were recorded on a four channel event recorder (Scientific Prototype Mfg. Corp., Model 4070J) and were scored for meal size and frequency. A meal was defined as no less than ten pellets separated by at least ten minutes from any other pellets. Pellets obtained outside of meals were counted and recorded as non-meal pellets. Spillage was measured and accounted for by subtracting the number of non-eaten pellets (inside or outside of the food tray) from the total number of pellets obtained.

Progressive Ratio

A modified progressive ratio schedule was utilized for two 24-hour periods, one pre-lesion and one post-lesion. During this schedule of reinforcement rats had free access to the lever and food tray, but were required to progressively work harder for pellets within a meal. The first pellet was received for one bar-press. The next pellet required two presses and three presses were required for the third pellet. This increase in the number of presses required to obtain a pellet continued until the animals reached an

FR-12 schedule of reinforcement, which they remained on for the duration of the meal. Upon the termination of the meal (10 minutes after the last pellet), the equipment reset back to the beginning of the progression.

Histology and Neurochemistry

Histology was performed according to the procedure described in Experiment 1. In this experiment, however, the frontal cortices were removed and assayed for NA levels using the spectrofluorometric assay technique described by Iwamoto, Lah, and Way (1976).

Protocol

Twenty-two rats (10-chronically implanted, 12-no prior surgery) were food deprived for 24 hours. They were then permanently placed in the feeding chambers and shaped to bar-press for pellets. This was followed by 15 days of adaptation. The rats were then placed on the progressive ratio schedule for 24 hours. Subsequent to a minimum of three days of recovery (depending upon availability of equipment), seven days of BL feeding behavior data were recorded. Bilateral lesions were then placed in the dorsal brainstem of all the chronically implanted, and eight of the non-implanted rats. The others received sham surgery. Twenty-one days of PL feeding behavior data were recorded. Subsequent to this, response to four days of quinine adulteration was measured by weight loss and change in food intake in 16 of the subjects. After several days of recovery, rats were again placed on the progressive ratio schedule. At the end of the experiment the animals were sacrificed and histology and neurochemistry were performed.

Each day at the onset of the light period, animals were weighed, their cages were serviced, spillage and daily water intake was measured, and the feeders were refilled.

The rats were grouped as either bilateral VLC-lesioned (see figure 11) or controls. The data was analyzed using a profile analysis (Morrison, 1976) for changes in food intake, water intake, body weight, number and size of meals, light-dark distribution of feeding, and response to quinine adulteration. The neurochemical and progressive ratio data were analyzed using a t-test. Correlations were performed between the magnitude of destruction to specific nuclei and the changes in pellet intake.

Results

Histology

The lesions in the chronically implanted rats were comparable in size to those in Experiment 1 (see figures 1, 2, 3, and 12); the lesions in the non-chronically implanted rats were smaller (see figures 13-16).

Eleven of the 22 rats had bilateral destruction within the VLC (see figure 11). The 11 control animals consisted of seven lesioned-controls and four shams.

The rats within the VLC group varied with respect to LC destruction. Figure 13 shows the lesions of a VLC rat with bilateral LC destruction. Figure 12 shows another VLC rat, with larger lesions, but only unilateral LC destruction. Other VLC rats had no destruction to the principal LC on either side (see figure 14).

Four of the seven lesioned control rats had unilateral destruc-

tion within the VLC. Figure 15 is an example of a lesioned control with unilateral VLC destruction. The left lesion in this subject is dorsolateral to the VLC; it is, however, impinging upon the dorsolateral tip of the LC. Figure 16 is an example of lesions that left the VLC intact bilaterally.

Data Analysis

Changes in feeding behavior in the subjects was not differentially affected by the two lesion procedures (PL1, $F=0.84$, $df=1,16$, $p>.10$; PL2, $F=2.13$, $df=1,16$, $p>.10$; PL3, $F=0.17$, $df=1,16$, $p>.10$). Therefore, they were combined for all subsequent analyses.

There were no significant differences between lesioned controls and shams on all measures of feeding behavior tested except for water intake (see appendix C). The two groups were therefore combined to form the control group on all measures except water intake. Appendix D contains the mean changes from BL during each week, PL for all measures that the analyses were performed upon.

Food intake and body weight. During PL1 the VLC rats significantly decreased their food intake ($F=11.16$, $df=1,20$, $p<.01$) and body weight ($F=4.51$, $df=1,20$, $p<.05$) as compared to controls. The food intake of the VLC group decreased 39.1% from BL while the controls had a 16.2% reduction (see figure 17). The VLC rats lost 6.4% of their body weight while the controls lost only 2.0% (see figure 18).

During PL2 the VLC rats increased their food intake from BL by 8.5% while the controls ate 97.9% of their BL levels ($F=2.90$, $df=1,20$, $p>.10$) (see figure 17). Both groups regained the lost body weight by the end of PL2 and weighed just over BL levels ($F=0.01$, $df=1,20$, $p>.10$) (see figure 18).

As shown in figure 17, during PL3 the VLC rats significantly ($F=10.77$, $df=1,20$, $p<.01$) increased their food intake (20.8% above BL) as compared to controls who were eating at BL levels. The mean body weight of the VLC rats increased to 105.3% of BL levels while the controls were at 102.75% by the end of PL3 (see figure 18). This difference, however, was not significant ($F=1.02$, $df=1,20$, $p>.10$).

Significant differences did occur between the groups in the changes of food intake ($F=10.63$, $df=3,18$, $p<.001$) and body weight ($F=5.41$, $df=3, 18$, $p<.01$) over time. Within the VLC group a significant decrease in food intake ($F=38.90$, $df=1,10$, $p<.0001$) and body weight ($F=11.17$, $df=1,10$, $p<.01$) occurred between BL and PL1. This was followed by a significant increase in food intake ($F=47.42$, $df=1,10$, $p<.0001$) and body weight ($F=54.26$, $df=1,10$, $p<.0001$) between PL1 and PL2. From PL2 to PL3 the VLC rats did not further increase their food intake significantly ($F=2.74$, $df=1,10$, $p>.10$), but did significantly increase their weight gain ($F=9.13$, $df=1,10$, $p<.05$).

Water intake. Water intake data was not recorded for two of the subjects. Accurate measures on these animals could not be attained because of large amounts of spillage during pre-lesion conditions. These two subjects were both from the VLC group.

Since significant differences occurred in the water intake changes between sham operated and lesion controls, they were not grouped for the water intake analyses. Significant differences in the change in water intake occurred between the three groups during PL1 ($F=5.20$, $df=2,17$, $p<.05$) and PL2 ($F=4.28$, $df=2,17$, $p<.05$), but not duirng PL3 ($F=0.53$, $df=2,17$, $p>.10$). The Hotelling-Lawley trace

indicated significant differences in the trends of the three groups ($F=3.81$, $df=6,28$, $p<.01$).

As compared to sham operated controls the VLC group had a significantly greater decrease in water intake during PL1 ($F=11.73$, $df=1,11$, $p<.01$). These groups did not differ during PL2 ($F=0.79$, $df=1,11$, $p>.10$) and PL3 ($F=0.04$, $df=1,11$, $p>.10$). There was a significant difference between the groups for the trends over time ($F=7.76$, $df=3,9$, $p<.01$).

Changes in water intake did not differ between the VLC group and lesioned controls ($F=1.51$, $df=1,14$, $p>.10$; $F=0.43$, $df=1,14$, $p>.10$; $F=1.12$, $df=1,14$, $p>.10$). The change in water intake over time between these two groups fell just short of significance ($F=3.43$, $df=3,12$, $p<.06$).

The VLC rats significantly decreased their water intake between BL and PL1 ($F=30.15$, $df=1,8$, $p<.001$). This was followed by a significant increase between PL1 and PL2 ($F=25.55$, $df=1,8$, $p<.001$). No significant change in water intake occurred between PL2 and PL3 ($F=2.00$, $df=1,8$, $p>.10$).

There was a large amount of variability within the VLC group with respect to changes in water intake. Although the hyperphagic rats as a group did not become significantly hyperdipsic, there was a significant correlation ($r=+0.72$, $p<.05$) between the change in food intake and the change in water intake from BL to PL3. The hyperphagic rats maintained their food/water ratio throughout the experiment. Compared to BL there was no significant difference in the food/water ratio between the hyperphagic and control groups ($F=1.64$, $df=1,18$, $p>.10$).

Meal Patterns. During BL conditions it was found that 95.75% of all pellets were consumed during meals. The mean number of daily meals for all subjects was 16.1 during BL. The mean meal size was 34.25 pellets.

The hypophagia in the VLC group during PL1 was characterized by a significant decrease in meal frequency ($F=4.88$, $df=1,20$, $p<.05$) with no change in meal size ($F=0.14$, $df=1,20$, $p>.10$) or the number of non-meal pellets ($F=1.29$, $df=1,20$, $p>.10$) as compared to controls.

During PL2 and PL3 there were no significant differences between the groups as compared to BL in meal frequency ($F=1.31$, $df=1,20$, $p>.10$; $F=0.04$, $df=1,20$, $p>.10$) or meal size ($F=1.94$, $df=1,20$, $p>.10$; $F=2.10$, $df=1,20$, $p>.10$). The VLC group, however, had a significantly higher increase in the number of non-meal pellets ($F=7.59$, $df=1,20$, $p<.05$; $F=6.26$, $df=1,20$, $p<.05$) (see figures 20-22).

No significant differences between the groups occurred over time for meal size ($F=2.08$, $df=3,18$, $p>.10$), meal frequency ($F=2.12$, $df=3,18$, $p>.10$) or non-meal pellets ($F=2.61$, $df=3,18$, $p<.10$). The non-meal pellet trend, however, approached significance.

Within the VLC group meal frequency significantly decreased from BL to PL1 ($F=26.60$, $df=1,10$, $p<.0005$). Meal frequency increased from PL1 to PL2 ($F=9.29$, $df=1,10$, $p<.05$) and further increased from PL2 to PL3 ($F=18.16$, $df=1,10$, $p<.005$).

Meal size did not change within the VLC group from BL to PL1 ($F=0.02$, $df=1,10$, $p>.10$) but did increase from PL1 to PL2 ($F=7.28$, $df=1,10$, $p<.05$). This increased meal size was not further enhanced, but maintained during PL3 ($F=0.31$, $df=1,10$, $p>.10$).

The number of non-meal pellets significantly increased from BL to PL1 ($F=21.13$, $df=1,10$, $p<.001$) and did not change during subsequent weeks ($F=0.35$, $df=1,10$, $p>.10$; $F=0.25$, $df=1,10$, $p>.10$) (see figures 20-22).

Light/dark feeding. Increases in feeding were observed in the hyperphagic rats (PL3) during both the light and dark parts of the cycle. As shown in Table 3, there were no changes in the proportion of feeding during either lighting period ($F=0.02$, $df=1,20$, $p>.10$). Throughout the experiment, all rats did approximately 70% of their feeding during the dark period. No differences in the proportion of feeding in the dark between the groups occurred over time ($F=1.50$, $df=3,18$, $p>.10$).

Quinine Adulteration. As shown in figures 23 and 24, all animals reduced their food consumption and lost weight during the four days of quinine adulteration. The difference in reductions between the groups was insignificant at all times.

The changes in food intake and body weight in response to quinine adulteration over time did not differ between groups ($F=0.71$, $df=4,9$, $p>.10$; $F=1.71$, $df=4,10$, $p>.10$). Both groups significantly decreased their pellet intake during the first day of quinine adulteration ($F=89.76$, $df=1,13$, $p<.0001$). During the following three days of quinine adulteration, the pellet intake did not significantly increase ($F=1.64$, $df=1,13$, $p>.10$; $F=0.74$, $df=1,13$, $p>.10$; $F=0.57$, $df=1,13$, $p>.10$).

Progressive Ratio

Due to equipment failure, progressive ratio data was not recorded for two of the subjects. One of these subjects was from each group.

Both groups decreased their pellet intake while on the progressive ratio schedule during pre- and post-lesion conditions. Pre-lesion, the decrease in intake from the previous day did not differ between groups ($t=0.93$, $df=18$, $p>.10$). Post-lesion, however, the VLC-lesioned rats had a significantly greater decrease in pellet intake ($t=2.42$, $df=18$, $p<.05$).

The number of bar-presses during the progressive ratio schedule did not differ between pre- and post-lesion for either the VLC-lesioned rats ($t=0.77$, $df=9$, $p>.10$) or the controls ($t=1.47$, $df=9$, $p>.10$).

Neurochemistry

The VLC-lesioned rats had a 19.04% reduction in cortical NA and the lesioned controls had a 16.78% reduction as compared to the non-lesioned controls ($t=0.04$, $df=14$, $p>.10$).

Within the hyperphagic animals there was no correlation between the magnitude of the hyperphagia and the cortical NA depletion ($r=0.17$, $p>.10$).

Lesions-Food Intake Correlations

Pearson correlation coefficients between change in pellet intake and the magnitude of destruction to specific nuclei indicated no significant correlations. Unlike the correlations involving other nuclei, the correlation between the subcoeruleus and pellet intake approached significance ($r=0.43$, $p<.10$) (see Table 4).

Discussion

This experiment indicated that the increased feeding in Experiment 1 was due to a hyperphagia, rather than hyperdipsia. Although

the food/water ratio was maintained in the hyperphagic rats, they became significantly hyperphagic, but not significantly hyperdipsic.

The data suggests that the hyperphagia may be due to a satiety deficit, rather than increased hunger. The progressive ratio data indicated that the hyperphagic rats did not work to maintain their increased food intake.

The reduction in food intake during quinine adulteration also indicates that the hyperphagic rats had a satiety deficit. Had they been hungrier than controls, they would have had a smaller reduction in feeding. It is possible that they did not reduce their intake more than controls (not finicky) because they were not obese.

It is interesting to note that the increased feeding was not reflected in changes in either meal size or meal frequency as compared to controls. The hyperphagic rats increased their "snacking" (non-meal pellets). Within the VLC group, however, meal size was significantly increased between PL1 and PL2. This is the same time that these animals began increasing their food intake.

The histology was again carefully analyzed and the area that best represented the bilateral destruction in the hyperphagic rats, that was intact at least unilaterally in the lesioned controls was selected. Figure 25 indicates that area. It is the dorsal part of the subcoeruleus and includes only the ventral tip of the LC. The magnitude of destruction to the subcoeruleus was again found to best predict the magnitude of the hyperphagia.

The cortical NA assays also indicated that destruction of the principal LC is not responsible for the hyperphagia. The hyperphagic

rats did not have a significantly larger reduction of cortical NA as compared to the lesioned controls. Furthermore, within the hyperphagic animals there was no significant correlation between cortical NA depletion and the magnitude of the hyperphagia.

General Discussion

Interpretation of Results

The data indicate that lesions within the area of the subcoeruleus result in hyperphagia. The area resulting in the hyperphagia included, and extends ventral and lateral to, the ventral tip of the principal LC.

The neurochemical data also indicates that the principal LC and its ascending projections through the DNB are not responsible for the hyperphagia. Had lesions to the principal LC been the primary cause of the hyperphagia, larger cortical NA depletions would have occurred in the hyperphagic animals.

Although there are some indications that the overeating is due to increased hunger, it is more probable that it is due to a satiety deficit. While on the progressive ratio schedule of reinforcement, the hyperphagic rats did not work harder to maintain their increased food intake.

Another indication that the hyperphagia was due to a satiety deficit rather than increased hunger is the reduction in feeding during quinine adulteration. Had the hyperphagic rats been hungrier, they would have had a smaller reduction in feeding than the controls.

The hyperphagic animals, however, did not appear finicky. They did not have a greater decrease than controls in food intake during quinine adulteration. The lack of finickiness in the hyperphagic rats may be due to their lack of obesity or to the intact state of the neural fibers mediating the finicky response in HYP hyperphagic animals. The fact that the hyperphagia was larger in magnitude in the first experiment, where the animals were maintained on a more palatable milk diet, indicates the possibility, however, of increased taste responsivity.

This satiety deficit is different than that resulting from VMH lesions as revealed by the intact diurnal feeding cycle and the meal pattern data. While maintained on liquid diets, HYP hyperphagic rats overeat by consuming larger meals; when fed pellets, they eat more meals. The hyperphagic rats in these studies increased their intake on the milk diet by eating more meals. When maintained on a solid food diet, they ate the same number and size meals as compared to controls, but snacked more frequently. As compared to their own BL, however, the hyperphagic rats in the second experiment increased their meal size. This apparent difference in meal pattern changes with the different diets, however, may be an artifact of the way a meal was defined.

While maintained on the milk diet, rats ate approximately 85 kcal/day. When fed pellets, their intake was approximately 115 kcal/day. Although their caloric intake was higher when maintained on pellets, the mean meal size was calorically larger when fed milk (9.24 kcal/meal vs. 6.85 kcal/meal). This difference is probably due to the bulk of the solid food as compared to the milk.

The criteria for milk meals, when defined calorically instead of behaviorally, is much less than that for a pellet meal. The minimum meal size of 10 pellets is equivalent to 2.0 kcal. The 10 lick criteria, however, is only 0.065 kcal. One pellet contains more calories that the minimum required for a milk meal and 308 licks is equivalent to the caloric intake of the minimum pellet meal. The increased meal frequency of the hyperphagic animals in the first experiment contained many small meals which were less than 308 licks.

If the minimum meal requirements are equated for both experiments and set at 2.0 kcal (as it was defined in the second experiment), the hyperphagic rats in both experiments overate by increasing snacking.

Changes in meal patterns in relation to the temporal occurrence of the increase in feeding also indicate that the hyperphagia may be due to a satiety deficit. In the first experiment significant increases in meal frequency within the LC-lesioned group occurred between BL and PL1. During this time, however, the animals did not increase their food intake. The increased feeding that occurred during PL2 and PL3 were not accompanied by any changes in meal frequency.

In the second experiment, significant increases in non-meal pellets occurred in the VLC group during PL1 (at which time they became hypophagic). During PL2, however, significant increases occurred in both food intake and meal size.

Unlike other hyperphagia syndromes which result from destruction to fibers entering the HYP, in which the rats overeat immediately after the lesion, the animals in these experiments did not become hyperphagic for at least one week after the lesion. This time period coincides with the time duration it takes for DBH reductions to occur in the HYP following LC lesions (Ross & Reis, 1974). This reflects the time duration required for axonal degeneration and further indicates that the effect is due to alterations of HYP loci caused by the hindbrain lesions as opposed to a separate hindbrain feeding system.

Another major difference between this hyperphagia and that resulting from VMH lesions is the delayed onset and reduced magnitude

of body weight gains. This is most apparent in the first experiment. During PL2 the LC-lesioned rats were hyperphagic, yet they were gaining weight at a slower rate than controls. It was not until PL3 that the hyperphagic rats increased their rate of body weight gain. This delayed weight gain is identical to that described by Grossman and Grossman (1977) following knife cuts to the rostral brainstem in the area of the intermediate bundle. Their hyperphagic animals began gaining weight faster than controls approximately 10 days after the lesions. As suggested by Grossman and Grossman, and indicated by the more rapid increase in number of licks as compared to milk intake, the hyperphagia at that time may be compensating for increased energy loss.

The hyperphagic syndrome resulting from subcoeruleus lesions is quite different than the one following VMH lesions. It has, however, many similarities to the hyperphagia reported by Ahlskog and Hoebel (1973) subsequent to lesions in the midbrain tegmentum. In both of these syndromes the rats have a smaller magnitude hyperphagia and less obesity as compared to VMH-lesioned rats, an intact diurnal feeding cycle, and do not appear finicky.

The hyperphagia reported by Ahlskog and Hoebel, which they believe is due to VNB destruction, has been shown to be distinct from HYP hyperphagia as opposed to a component of it (Ahlskog et al., 1975). The data from these experiments do not indicate whether the hyperphagia resulting from subcoeruleus lesions is a component of HYP hyperphagia or a separate syndrome. If it is a component, it is likely that the intermediate bundle is one of several pathways destroyed by VMH lesions.

However, if it is a distinct syndrome, it is likely that the hyperphagia resulting from midbrain lesions is due to intermediate bundle, rather than VNB damage. In accordance with this second hypothesis, I predict that lesions to the cell group A_5 (the major source of the VNB) will not alter food intake.

Implications for Sleep Research

Rapid eye movement (REM) sleep is a period during which CNS activation occurs along with rapid conjugate eye movements, muscle atonia, and behavioral quiescence. Steiner and Ellman (1972) found that a reciprocal relationship exists between REM sleep and HYP ICSS such that REM sleep deprivation reduces ICSS thresholds and 1.5 hours of ICSS reduces REM rebound in REM deprived rats. Based upon this finding along with data indicating that (a) electrodes that elicit SBB are almost always ICSS sites (Margules & Olds, 1962), and (b) many waking behaviors that are elicited by HYP stimulation are altered by REM sleep deprivation (Dement, 1965), they hypothesized the existence of an ICSS neural network which is involved in the regulation of motivated behaviors. This network, they suggested, is part of a neural network activated during REM sleep. From this hypothesis they predicted that nuclei in the hindbrain that are involved in initiating aspects of REM sleep are ICSS sites.

LC and REM sleep. Neuroanatomically, the area of the LC has been implicated as the CNS site responsible for the triggering and maintenance of aspects of REM sleep. Jouvet (1967) demonstrated that in cats, discrete lesions in different parts of the LC disrupted different components of REM sleep. Bilateral lesions of the caudal third

of the LC suppressed the motor inhibition characteristic of REM sleep. These lesions, however, did not affect other aspects of REM such as activated EEG, PGO activity[1] and rapid eye movements. More extensive bilateral lesions, which destroyed the caudal half of the LC along with the subcoeruleus, disrupted the occurrence of other phasic aspects of REM sleep. He did find, however, that some PGO activity (which normally occurs primarily during REM) occurred during non-REM sleep (NREM). These lesions caused about a 30 percent decrease of NA in the forebrain without any alteration of the serotonin (5-HT) or DA levels. Control lesions placed ventral, medial, lateral or caudal to the area did not affect REM sleep or forebrain NA levels. According to Jouvet (1973), the neurons in the anterior third of the LC do not participate in REM mechanisms.

Jouvet (1973) has also examined the effects of lesions to the NA pathways, ascending from the LC, on the sleep-wake cycle. Bilateral destruction of the DNB at the level of the isthmus induced a temporary hypersomnia with increases of both NREM and REM. He believes that this was due to the suppression of NA fibers controlling the raphe system. More rostral DNB lesions decrease the duration of cortical arousal, thus increasing sleep. There is, however, no selective increase in REM.

Lesions to the region of the intermediate bundle described by Maeda and Shimizu (1972) suppress PGO activity in the lateral geniculate and occipital cortex (Laurent, Cespuglio, & Jouvet, 1972). This indicates that the ventral LC or the subcoeruleus may be responsible

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[1] PGO activity is monophasic spiking that can be recorded in the pons, lateral geniculate, and occipital cortex. These phasic events occur primarily during REM sleep and their occurrence is highly correlated with the occurrence of rapid eye movements.

for triggering those phasic REM events.

Jones, Harper and Halaris (1977c) also examined the effect of LC lesions on the sleep-wake cycle. Similarly, they found suppression of only the motor inhibition during REM with posterior LC lesions. They believe, however, that the muscle atonia is mediated by non-LC, cholinergic mechanisms rather than NA because they were unable to replicate this finding using 6-OH-DA lesions.

Jones et al. (1977c) found that more rostral LC lesions disrupted the occurrence (reduced but did not eliminate) of PGO spikes and dissociated them from REM, but did not affect the tonic activated EEG. They believe that these effects may possibly be NA mediated.

With the use of an electrical stimulation technique, the LC has also been implicated in the mediation of REM sleep. Rats allowed to self-stimulate, bilaterally, in the LC, had decreased REM sleep and little or no REM rebound (Spielman, Davis, Marks, Halperin, Schwartz, Halperin, Steiner, & Ellman, 1974). This indicates that the LC stimulation was, in some way, replacing the need for REM sleep.

Several unit recording studies have been performed which investigated the changes of firing rates of neurons in the brainstem during the sleep-wake cycle. Chu and Bloom (1973) found that LC neurons increase their firing rates specifically during REM as compared to NREM and quiet waking. This further indicated that the LC is in some way involved in the maintenance of REM sleep. Subsequent to that, however, Chu and Bloom (1974) reported that many neurons within the LC region decrease their firing rate selectively during REM. This indicates that there is more than one population of cells within the LC area.

McCarley and Hobson (1971) report selective decreases in firing rates of LC units with REM onset while increased discharge rates occur in the neurons of the gigantocellular tegmental field (FTG). Based on this data, they have put forth a model in which the LC inhibits REM sleep and FTG neurons. They believe that the FTG cells are the REM generators (Hobson, McCarley & Wyzinski, 1975).

Siegel and McGinty (1977) have been critical of the notion that FTG cells are REM generator cells and believe that McCarley and Hobson's findings are an artifact of their unit recording procedure. Throughout the recording, McCarley and Hobson's animals' heads were restrained. Siegel and McGinty clearly demonstrated, in unrestrained animals, that FTG cells fire in response to certain head and neck movements. Twitching movements of these types are frequently seen during REM sleep and are probably the cause of the increased FTG firing during that state.

Although critical of the recording technique and model put forth by Hobson and McCarley, Siegel and McGinty have also found that most units in the region of the LC turn off during REM sleep.

The lesion, stimulation, and unit recording data all indicate that the LC is involved in the mediation of some aspects of REM sleep. The more recent unit recording data indicate that during REM sleep, the majority of the neurons in the LC stop firing. It is possible that this "turning off" of LC neurons, may be critical to the initiation of REM sleep.

LC and ICSS. Since the LC appears to be a primary site involved in the initiation of aspects of REM sleep, according to Steiner and

Ellman's (1973) prediction, it should be an ICSS site. ICSS behavior has been elicited from electrodes chronically implanted in the DBS in and around the LC (Crow, Spear & Arbuthnott, 1972; Ellman, Ackermann, Farber, & Steiner, 1973; Sinnamon, Shaw, Amaral, & Woodward, 1978). Controversy exists, however, as to whether or not the LC is the neuroanatomical site responsible for maintaining ICSS from the DBS (Amaral & Routtenberg, 1975; van der Kooy & Phillips, 1977). Recent data seem to suggest that several DBS loci may support ICSS (Clavier, Fibiger, & Phillips, 1976; Sinnamon et al., 1978). These investigators reported both positive and negative ICSS results from different electrodes within the same neuroanatomical structure. They found no DBS structure which sustained ICSS 100 percent of the time. Sinnamon et al. found the highest percentage of ICSS eliciting electrodes ventrolateral to the nucleus LC. They suggested that ICSS near the LC may be dependent upon activation of NA fibers, not from the dorsal LC, but from the ventral LC, which go to the diencephalon. Clavier et al. (1976) found that DNB lesions did not affect DBS ICSS. Because of this, they also believe that the rostral projections of the LC to the telencephalon are not crucial to DBS ICSS. According to Jouvet (1973) these rostral projections are also not crucial to the maintenance of aspects of REM sleep.

Using various ICSS techniques, functional connections have been demonstrated to exist between LC ICSS sites and some HYP ICSS sites. LC lesions have been reported to facilitate ICSS in some HYP loci (Farber et al., 1976; Koob, Balcom, & Meyerhoff, 1976) while abolishing it in others (Farber, et al., 1976).

Interaction studies, which measured ICSS behavior elicited from stimulation to the area of the LC and HYP simultaneously, found that response rates were significantly higher than the sum of the rates elicited from the two loci individually (Ellman, Ackermann, Bodnar, Jackler, & Steiner, 1975).

Changes in ICSS rates were also examined using a pulse-pair stimulation technique with one pulse stimulating the area of the LC and the other the HYP. In some HYP loci the response rates were dependent upon which site (LC or HYP) received the first pulse, while in other HYP loci, the order made no difference (Bodnar, Ellman, Ackermann, Greenblatt, Steiner, & Coons, 1975). This again indicates that LC-HYP connections are not uniform, but dependent upon the specific locus within the HYP.

REM sleep and behavior. Attempts to understand the significance of REM sleep have led investigators to study changes in various behaviors in response to REM deprivation. REM deprivation has been found to result in what appears to be an increased "need" for REM sleep. REM deprived animals increase their number of attempts to enter REM sleep, have shorter latencies to REM onset, and have increased amounts of REM when allowed to sleep without interruption (for review, see Webb, 1969).

REM deprivation has been found to increase spontaneous motor activity (Albert, Acala, & Siegel, 1970; Dement, 1965) and various measures of aggression (Ferguson & Dement, 1969; Morden, Conner, Mitchell, Dement, & Levine, 1968; Sloan, 1972). It has also been shown to decrease hypothalamic ICSS thresholds and to increase press-

ing rates at most intensities (Steiner & Ellman, 1972). Recent data (Halperin, Halperin, Villegas, Daren, Steiner, & Ellman, 1977) has shown that REM deprivation decreases stimulus-bound eating (SBE) thresholds.

It is interesting to note that d-amphetamine (AMPH), which is a sympathomimetic agent, has behavioral effects on the above measures which are identical to those following REM deprivation (Ellman, Ackermann, Bodnar, Jackler, & Steiner, 1976; Iverson & Iverson, 1975; Lal, Nesson, & Smith, 1970; Stein, 1964; Steiner & Stokely, 1973).

LC and behavior. Many studies have examined behavioral changes in response to bilateral LC lesions. Bilateral LC lesions have been reported to decrease aggression (Eison, Stark, & Ellison, 1977), activity levels (Eison et al., 1977; Geyer, Segal, & Mandell, 1976), and sensitivity to pain (Ackermann, Bodnar, Kelly, & Glusman, 1977), while increasing social grooming and mounting behavior (Eison et al., 1977).

Studies examining the effect of bilateral LC lesions on feeding and drinking behavior have yielded inconsistent data and have been difficult to interpret. While studying the effects of LC lesions on social behavior, Eison et al. (1977) noted that LC-lesioned rats spent more time on the feeding tray and gained more weight than controls; however, they did not measure actual food intake. Another group (Osumi et al., 1975) reported hyperdipsia and a temporary hypophagia in response to bilateral LC lesions in rats. This temporary hypophagia (similar to that in Experiment 2) may have been a result of the non-specific effects of the surgical procedures; the animals were

sacrificed only seven days after the lesions, during which time they were still exhibiting daily increases in food intake. A recent study in monkeys (Redmond, Huang, Snyder, Mass, and Baulu, 1977) reported a long-lasting hyperphagia in response to bilateral LC destruction.

Behavioral significance of REM sleep. If neurons in the LC fire at slower rates selectively during REM sleep, REM deprivation would result in increased LC firing throughout the day. Conversely, LC lesions result in decreased discharge of these neurons. Based upon this, LC lesions should result in behavioral effects opposite to those following REM deprivation.

AMPH, a drug which is a strong REM suppressant (Rechtschaffen & Maron, 1974) and is believed to increase the synaptic availability of NA (Carlsson, Fuxe, Hamberger, & Lindquist, 1966), produces behavioral effects similar to those reported in response to REM deprivation and opposite to those reported in response to LC lesions.

It has been found that both REM deprivation and AMPH administration increase spontaneous motor activity (Albert et al., 1970; Dement, 1965; Iverson & Iverson, 1975), while LC lesions reduce activity levels (Eison et al., 1977; Geyer et al., 1976). REM deprivation and AMPH both increase various measures of aggression (Iverson & Iverson, 1975; Morden et al., 1968; Sloan, 1972), while LC lesioned rats have been reported to fight less than controls (Eison et al., 1977). Both REM deprivation and AMPH have been reported to decrease HYP ICSS thresholds (Stein, 1964; Steiner & Ellman, 1972) while LC lesions abolish ICSS in at least some HYP loci (Farber et al., 1976). Recent data (Halperin et al., 1977) have demonstrated that REM deprivation increases SBE

thresholds which implies an anorexic effect similar to that of AMPH (Iverson & Iverson, 1975). The data from these experiments continue to follow the pattern by evoking behavioral effects opposite to those of AMPH and REM deprivation by increasing ad libitum feeding in rats.

Halperin et al. (1977) suggested that the behavioral effects of REM deprivation are mediated by sympathetic nervous system activation. The behavioral responses to REM deprivation of increased activity and aggression, along with an inhibition of feeding, support this hypothesis. Snyder (1969) explains the evolution of REM sleep by suggesting that naturally occurring REM deprivation (in response to environmental stress) serves as a mechanism that prepares the organism for environmental challenge. This preparatory response could be mediated through sympathetic nervous system activation in response to REM deprivation.

Appendix A

Comparisons Between Non-LC-Lesioned Groups in Experiment 1

Variable	Week	F	df	p
Milk intake	PL1	2.35	2,3	>.10
	PL2	3.35	2,3	>.10
	PL3	1.54	2,3	>.10
Number of licks	PL1	0.07	2,2	>.10
	PL2	0.07	2,2	>.10
	PL3	0.63	2,2	>.10
Body weight	PL1	14.49	2.3	<.05
	PL2	3.55	2,3	>.10
	PL3	27.14	2,3	<.05
Meal frequency	PL1	2.79	2,2	>.10
	PL2	3.59	2,2	>.10
	PL3	0.99	2,2	>.10
Meal size	PL1	0.93	2,2	>.10
	PL2	0.64	2,2	>.10
	PL3	0.80	2,2	>.10

Appendix B

Mean Changes From BL Used for Analyses in Experiment 1

Variable	Cond.	LC	Control	Sham	FL	A-V
Intake (ml)	PL1	-3.41	-13.07	-	-	-
	PL2	10.61	-1.11	-	-	-
	PL3	17.08	-2.75	-	-	-
Licks	PL1	724.7	-3030.2	-	-	-
	PL2	4562.0	-146.0	-	-	-
	PL3	5269.4	-1392.8	-	-	-
Weight (gm)	PL1	-7.3	-	-4.0	4.0	22.5
	PL2	-4.0	-	6.0	27.5	44.0
	PL3	18.8	-	6.5	20.0	66.5
Meals/day	PL1	6.85	1.23	-	-	-
	PL2	6.56	-0.46	-	-	-
	PL3	6.53	0.48	-	-	-
Licks/meal	PL1	-586.3	-317.0	-	-	-
	PL2	-329.3	113.0	-	-	-
	PL3	-236.3	-137.7	-	-	-
% dark intake	PL1	-10.2	-1.7	-	-	-
	PL2	2.9	2.3	-	-	-
	PL3	0.6	1.6	-	-	-
% dark licks	PL1	-7.7	-2.5	-	-	-
	PL2	4.0	3.4	-	-	-
	PL3	2.5	2.2	-	-	-

Variable	Cond.	LC	Control	Sham	FL	A-V
% intake change	Q1	-39.5	-62.5	-	-	-
	Q2	-13.2	-31.3	-	-	-
	Q3	-23.0	-27.5	-	-	-
	Q4	12.6	-19.5	-	-	-

Appendix C

Comparisons Between Sham Operated and Lesioned Controls in Experiment 2

Variable	Week	F	df	p
Pellet intake	PL1	0.08	1,9	>.10
	PL2	0.23	1,9	>.10
	PL3	0.00	1,9	>.10
Body weight	PL1	0.25	1,9	>.10
	PL2	1.36	1,9	>.10
	PL3	0.40	1,9	>.10
Water intake	PL1	5.10	1,9	>.05
	PL2	6.00	1,9	<.05
	PL3	1.96	1,9	>.10
Meal frequency	PL1	0.70	1,8	>.10
	PL2	1.08	1,8	>.10
	PL3	1.72	1,8	>.10
Meal size	PL1	0.09	1,9	>.10
	PL2	0.47	1,9	>.10
	PL3	1.44	1,9	>.10
Non-meal pellets	PL1	2.70	1,8	>.10
	PL2	1.28	1,8	>.10
	PL3	0.98	1,8	>.10

Appendix D

Mean Changes From BL Used for Analyses in Experiment 2

Variable	Cond.	VLC	Control	Sham	Les. Con.
Pellet intake	PL1	-208.78	-85.38	-	-
	PL2	47.40	-11.21	-	-
	PL3	116.13	-4.66	-	-
Weight (gm)	PL1	-22.09	-6.82	-	-
	PL2	3.82	3.00	-	-
	PL3	18.18	9.18	-	-
H_2O intake (ml)	PL1	-20.93	-	-0.72	-13.89
	PL2	-2.80	-	3.85	-6.55
	PL3	2.95	-	4.61	-4.47
Meals/day	PL1	-7.2	-3.7	-	-
	PL2	-3.6	-1.9	-	-
	PL3	-1.4	-1.1	-	-
Pellets/meal	PL1	-0.5	1.0	-	-
	PL2	13.8	2.7	-	-
	PL3	10.5	1.0	-	-
Non-meal pellets	PL1	19.5	8.0	-	-
	PL2	16.8	2.8	-	-
	PL3	14.7	5.7	-	-
% dark intake	PL1	1.02	-3.75	-	-
	PL2	2.38	-0.53	-	-
	PL3	1.68	2.30	-	-

Variable	Cond.	VLC	Control	Sham	Les. Con.
% intake	Q1	-31.23	-39.28	-	-
	Q2	-29.70	-27.82	-	-
	Q3	-26.05	-23.74	-	-
	Q4	-36.90	-19.01	-	-
% Body weight	Q1	-3.11	-3.98	-	-
	Q2	-3.11	-4.13	-	-
	Q3	-3.42	-4.12	-	-
	Q4	-3.96	-3.60	-	-

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Table 1

Percent of Milk Intake and Licks in the Dark

		Milk Intake				Licks			
		BL	PL1	PL2	PL3	BL	PL1	PL2	PL3
LC-Lesioned	$\bar{X}$	73.25	63.06	76.16	73.89	71.70	63.99	75.73	74.16
	S.E.M.	3.27	5.91	2.15	2.49	3.34	5.99	2.93	3.06
Controls	$\bar{X}$	70.88	69.25	73.18	72.51	68.64	66.09	72.03	70.85
	S.E.M.	1.63	6.12	3.37	3.69	1.96	6.09	4.01	3.63

Table 2

Pearson Correlation Coefficients for the 10 Lesioned Subjects in Experiment 1

	% DTN	% TMN	% Sub.	% BL Intake	% BL Licks
% LC	0.9132	0.9671	0.2084	0.6709	0.8492
	p=.001	p=.001	p=.563	p=.034	p=.002
% DTN		0.8282	0.0077	0.5028	0.7738
		p=.003	p=.983	p=.139	p=.009
% TMN			0.2278	0.6896	0.8514
			p=.527	p=.027	p=.002
% Sub.				0.7896	0.4938
				p=.007	p=.147
% BL Intake					0.8401
					p=.002

Table 3

Percent of Food Intake in the Dark

		BL	PL1	PL2	PL3
VLC-Lesioned	$\bar{X}$	69.40	70.42	71.78	71.08
	S.E.M.	2.98	4.46	2.26	2.10
Controls	$\bar{X}$	70.08	66.33	69.55	72.38
	S.E.M.	2.62	2.76	2.78	2.50

Table 4

Pearson Correlation Coefficients

for the 18 Lesioned Subjects in Experiment 2

	% DTN	% TMN	% Sub.	% BL Intake
% LC	0.8127	0.9650	-0.0022	0.1440
	p=0.001	p=0.001	p=0.993	p=0.569
% DTN		0.7526	-0.1120	0.2272
		p=0.001	p=0.658	p=0.365
% TMN			0.1374	0.1429
			p=0.587	p=0.572
% Sub.				0.4266
				p=0.077

Figure Captions

Figure 1. Schematic representation of the bilateral LC lesions in rat 84J. LC=locus coeruleus; TMN-trigeminal motor nucleus; MLF= medial longitudinal fasciculus; DTN=dorsal tegmental nucleus; BC= brachium conjunctivum; DR=dorsal raphe nucleus; IV=fourth ventricle.

Figure 2. Schematic representation of the bilateral FL lesions in rat 38K. LC=locus coeruleus; TMN-trigeminal motor nucleus; MLF= medial longitudinal fasciculus; DTN=dorsal tegmental nucleus; BC= brachium conjunctivum; IV= fourth ventricle.

Figure 3. Schematic representation of the bilateral A-V lesions in rat 21K. LC=locus coeruleus; TMN-trigeminal motor nucleus; MLF= medial longitudinal fasciculus; DTN=dorsal tegmental nucleus; BC= brachium conjunctivum; DR=dorsal raphe nucleus; ML=medial lemniscus; IV=fourth ventricle.

Figure 4. Schematic indicating the maximal extent of the lesions for all the animals in each group.

Figure 5. The mean percent of baseline milk intake for LC-lesioned and control rats during post-lesion weeks one, two, and three. Vertical lines represent the S.E.M.

Figure 6. The mean percent of baseline number of licks for LC-lesioned and control rats during post-lesion weeks one, two, and three.

Figure 7. The mean body weight, in grams, for LC-lesioned and control rats during the last day of baseline, and post-lesion weeks one, two, and three.

Figure 8. The mean number of daily meals for LC-lesioned and control rats during baseline, and post-lesion weeks one, two, and three.

Figure 9. The mean meal size of LC-lesioned and control rats during baseline and post-lesion weeks one, two, and three.

Figure 10. The mean percent of pre-quinine milk intake for LC-lesioned and control rats during quinine days one, two, three, and four.

Figure 11. Schematic representing the VLC. LC=locus coeruleus; TMN=trigeminal motor nucleus; DTN=dorsal tegmental nucleus; IV=fourth ventricle.

Figure 12. Schematic representation of the bilateral VLC lesions in rat 86K. This animal had unilateral LC destruction. LC=locus coeruleus; DTN-dorsal tegmental nucleus; TMN=trigeminal motor nucleus; BC=brachium conjunctivum; DR=dorsal raphe; IV-fourth ventricle.

Figure 13. Schematic representation of the bilateral VLC lesions in rat 28L. This animal also had bilateral LC destruction. DTN= dorsal tegmental nucleus; TMN=trigeminal moror nucleus; DR=dorsal raphe nucleus; IV=fourth ventricle.

Figure 14. Schematic representation of bilateral VLC lesions in rat 30L. This animal had no LC destruction. LC=locus coeruleus; DTN-dorsal tegmental nucleus; TMN=trigeminal motor nucleus; DR=dorsal raphe nucleus; IV=fourth ventricle.

Figure 15. Schematic representation of the unilateral VLC lesion in rat 23L. LC=locus coeruleus; TMN=trigeminal motor nucleus; DTN= dorsal tegmental nucleus; IV=fourth ventricle.

Figure 16. Schematic representation of the lesions in rat 25L. Both lesions are outside the VLC. LC=locus coeruleus; DTN=dorsal tegmental nucleus; TMN=trigeminal motor nucleus; DR=dorsal raphe nucleus; IV=fourth ventricle.

Figure 17. The mean percent of baseline pellet intake for VLC-lesioned, lesioned control, and sham rats during post-lesion weeks one, two, and three.

Figure 18. The mean percent of baseline body weight in VLC-lesioned and control rats on the last day of post-lesion weeks one, two, and three.

Figure 19. The mean percent of baseline water intake in VLC-lesioned and control rats during post-lesion weeks one, two, and three.

Figure 20. The mean number of daily meals for VLC-lesioned and control rats during baseline and post-lesion weeks one, two, and three.

Figure 21. The mean meal size for VLC-lesioned and control rats during baseline, and post-lesion weeks one, two, and three.

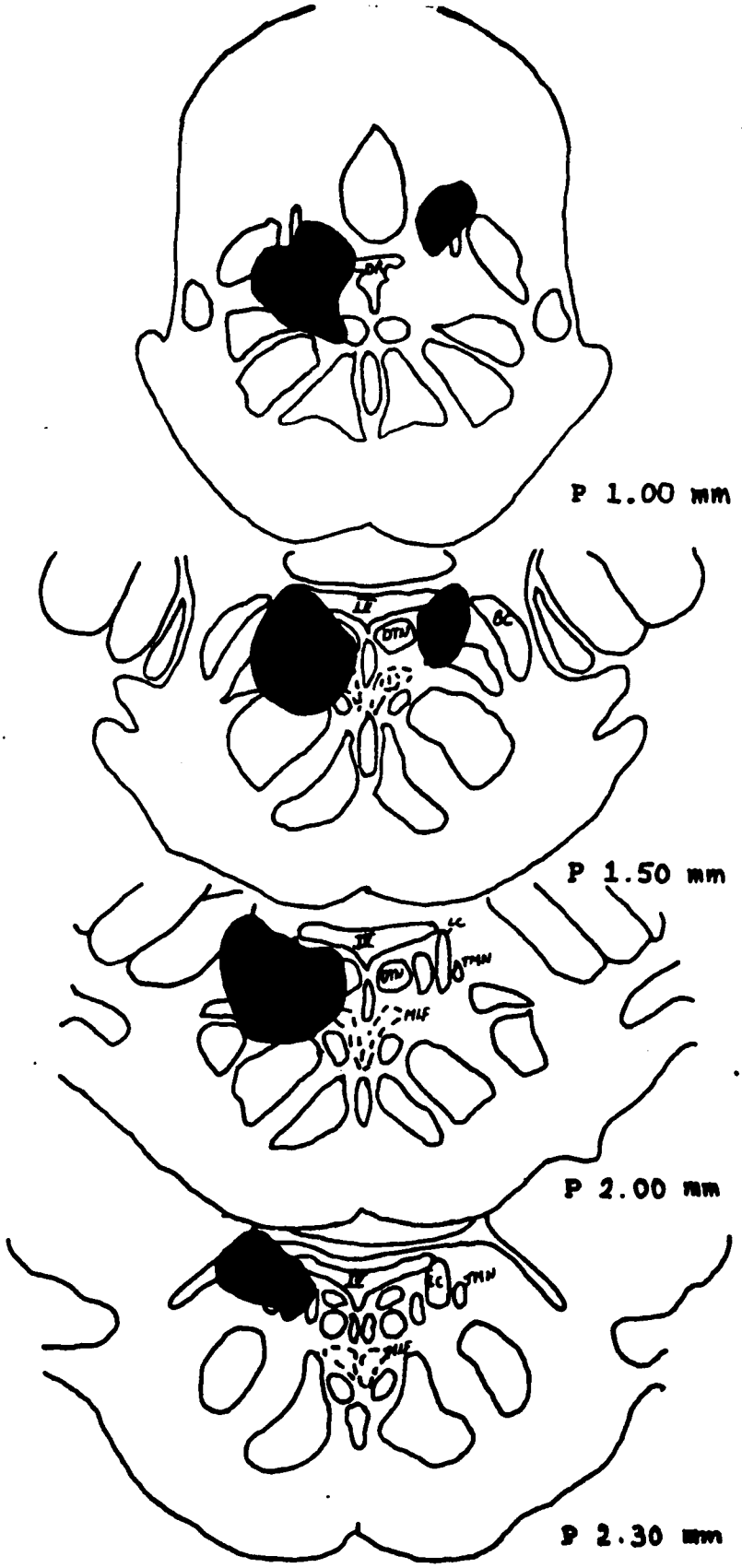
Figure 22. The mean number of non-meal pellets for VLC-lesioned and control rats during baseline, and post-lesion weeks one, two, and three.

Figure 23. The mean percent of pre-quinine pellet intake in VLC-lesioned and control rats during quinine adulteration days one, two, three, and four.

Figure 24. The mean percent of pre-quinine body weight in VLC-lesioned and control rats during quinine adulteration days one, two, three, and four.

Figure 25. The area representative of the bilaterally destroyed loci in the hyperphagic rats that was intact at least unilaterally in the lesioned controls.

Figure 1



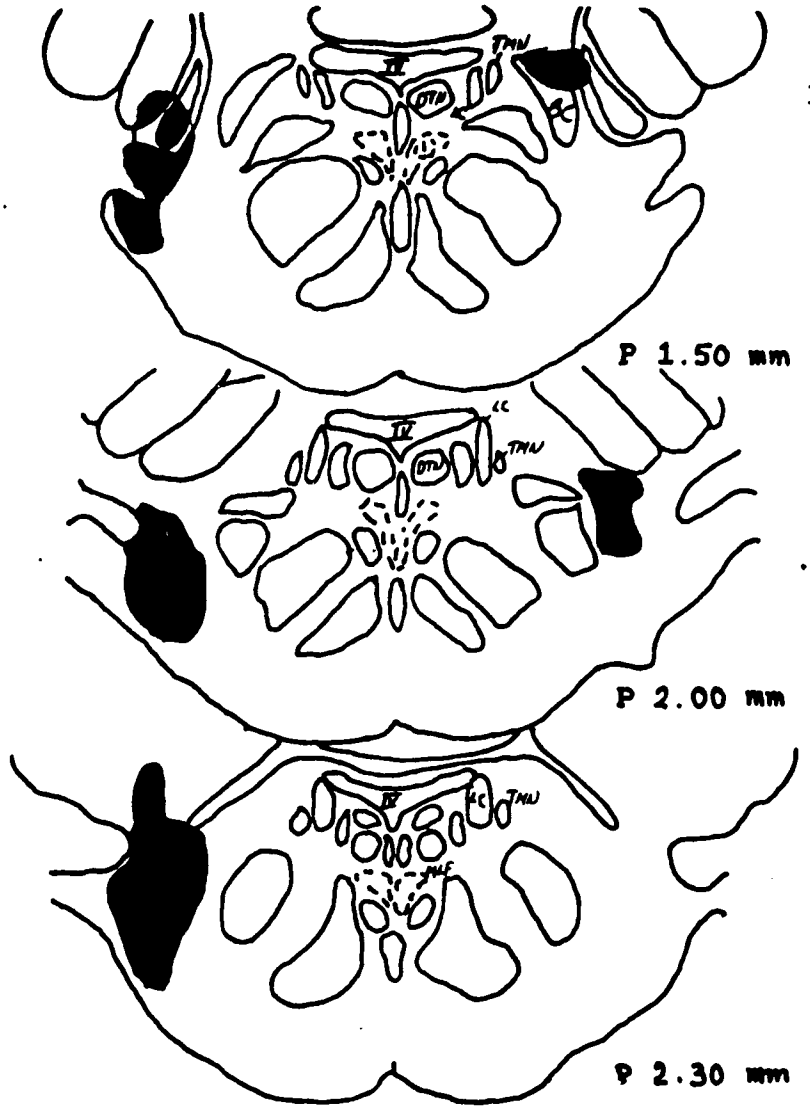
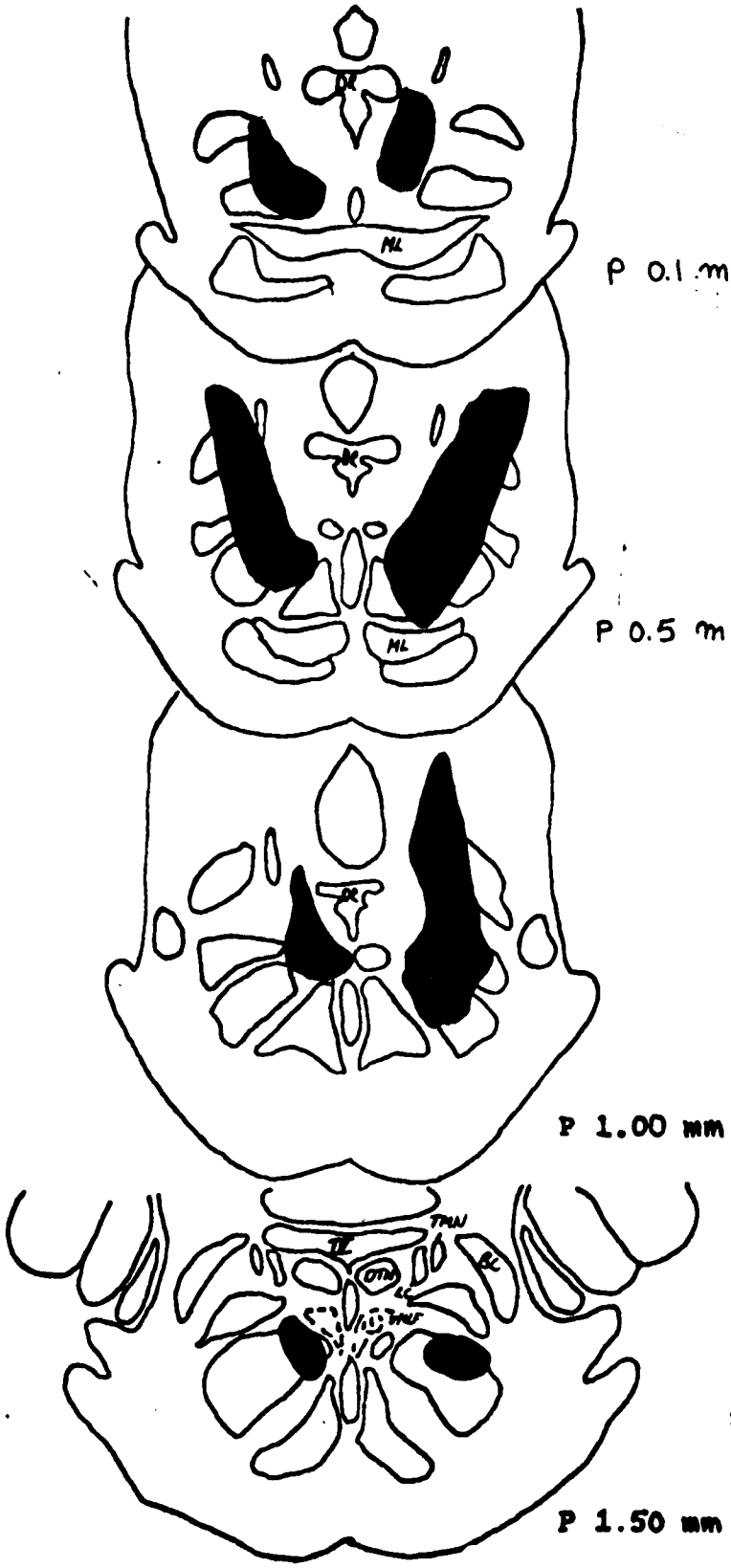


Figure 2

Figure 3



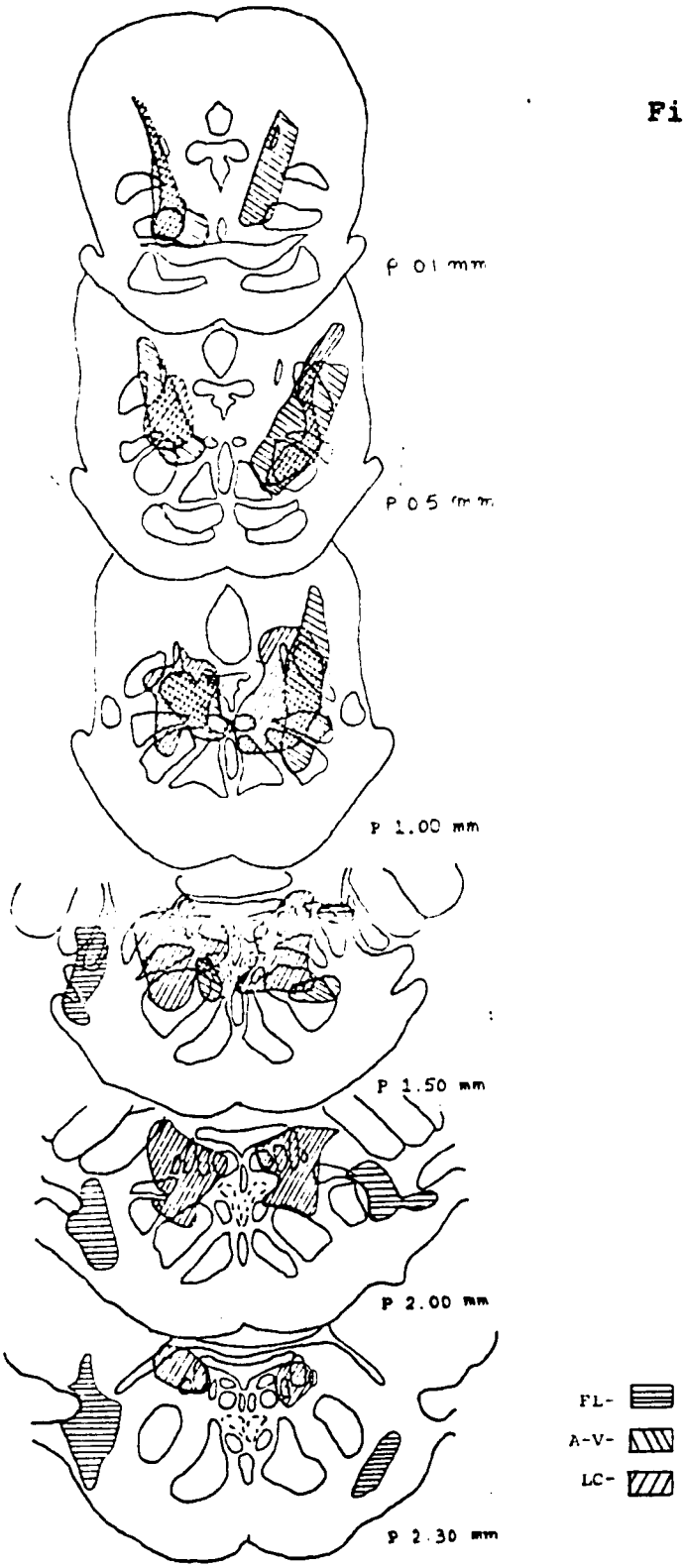


Figure 4

Figure 5

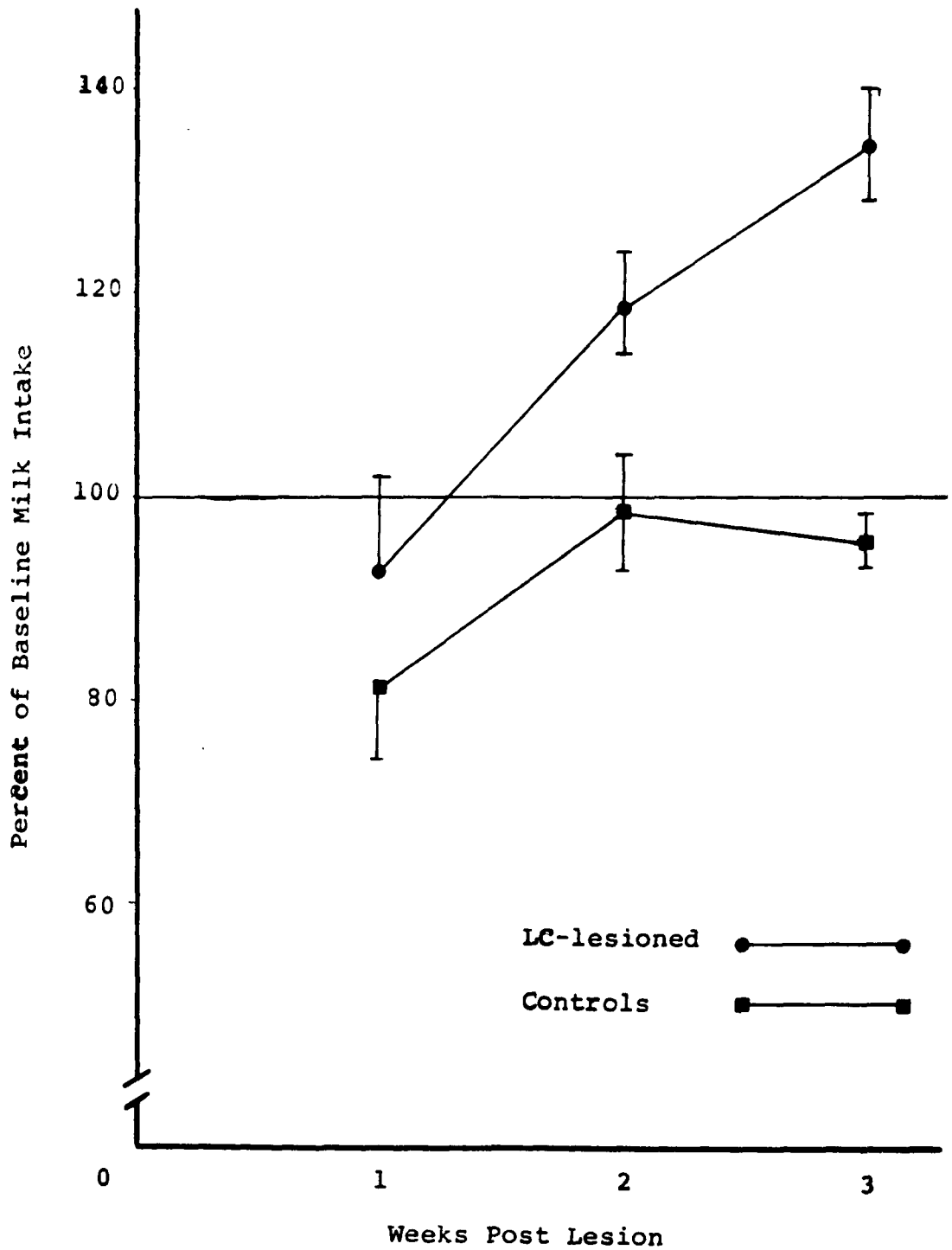

140
120
100
80
60
0
Percent of Baseline Milk Intake
1
2
3
Weeks Post Lesion
LC-lesioned
Controls

Figure 6

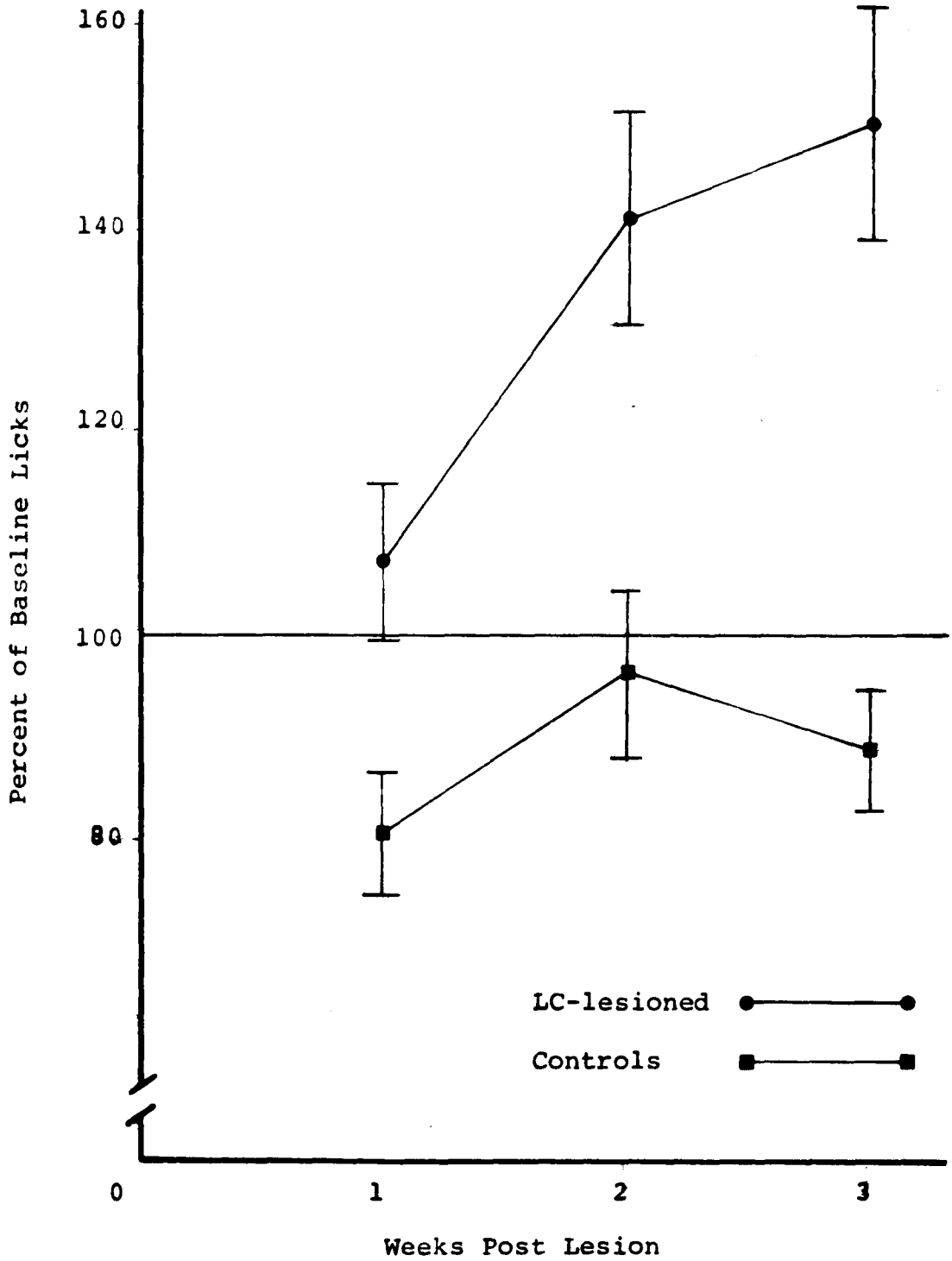
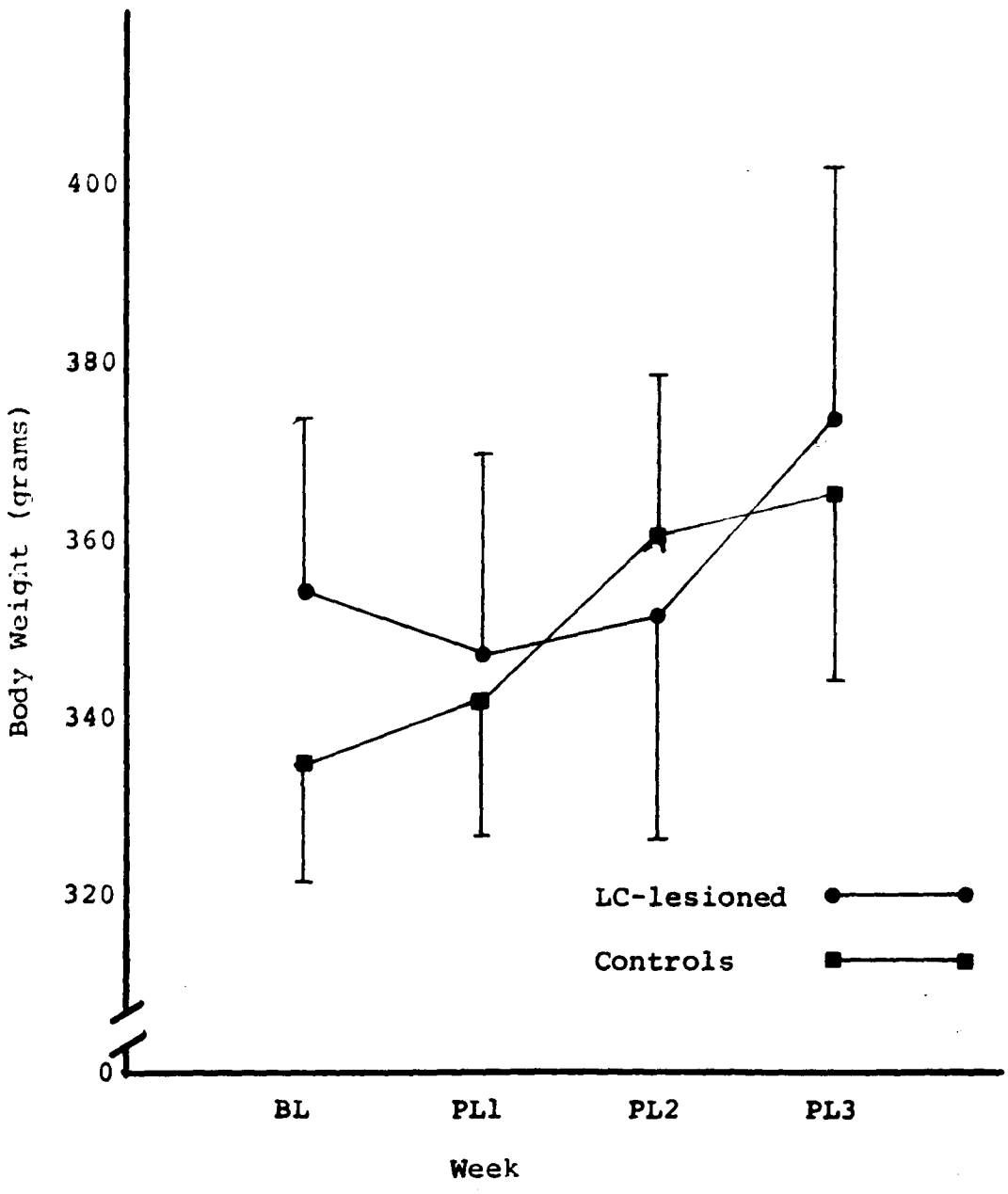

160
140
120
100
80
Percent of Baseline Licks
LC-lesioned
Controls
0
1
2
3
Weeks Post Lesion

Figure 7


400
380
360
340
320
0
Body Weight (grams)
BL
PL1
PL2
PL3
Week
LC-lesioned
Controls

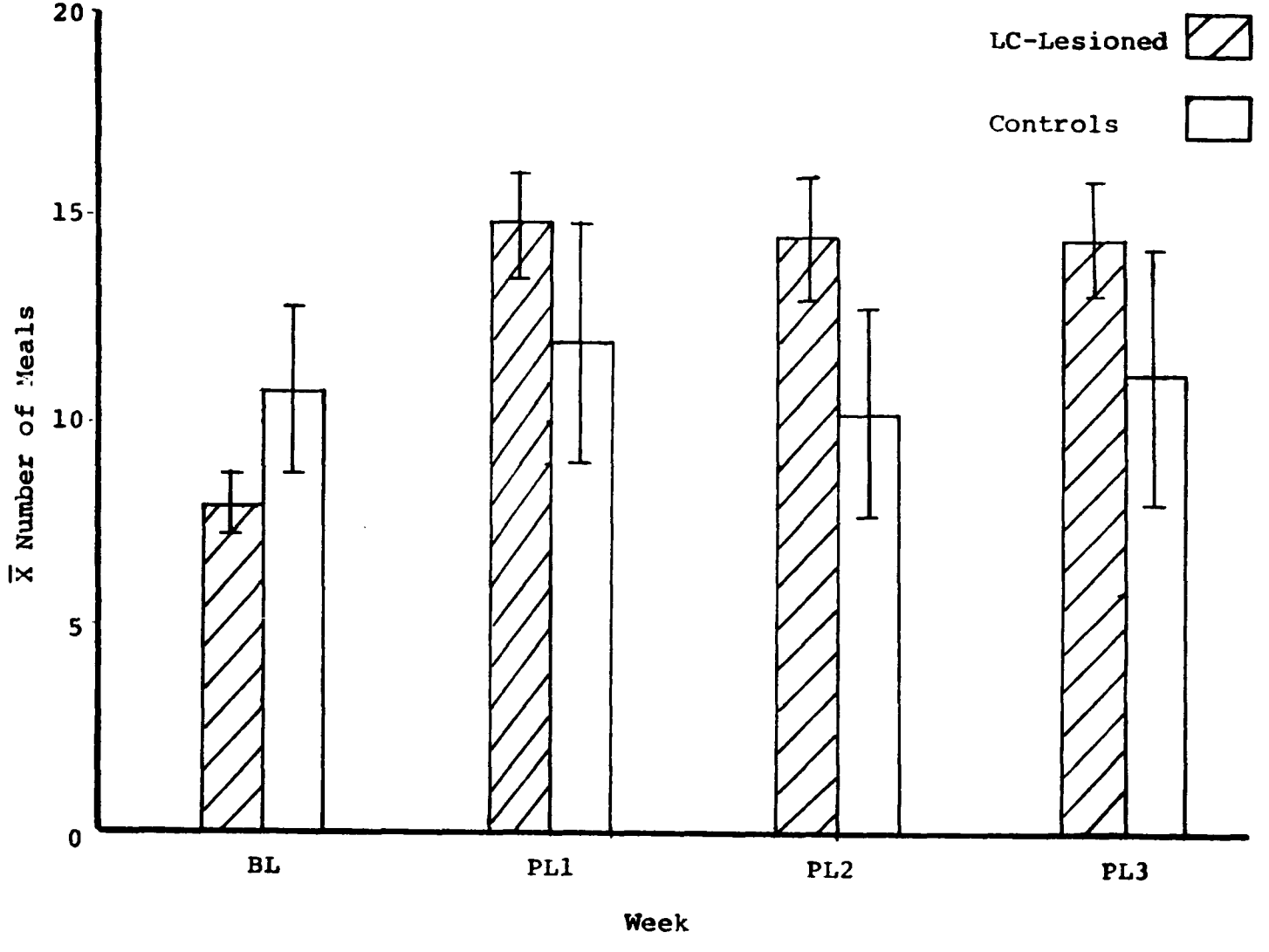

20
15
10
5
0
$\bar{X}$ Number of Meals
LC-Lesioned
Controls
BL
PL1
PL2
PL3
Week

Figure 8

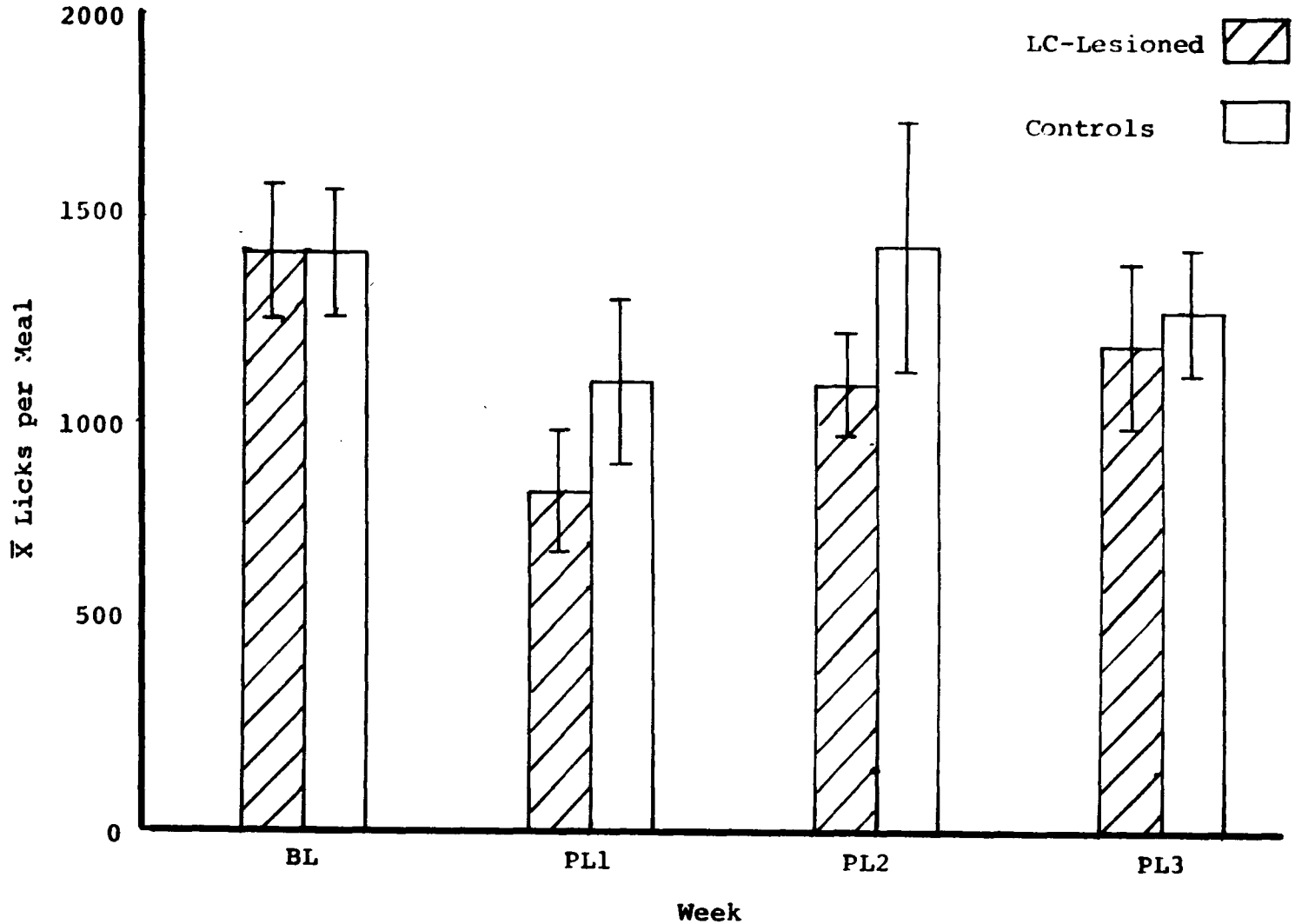

2000
1500
1000
500
0
X̄ Licks per Meal
LC-Lesioned
Controls
BL
PL1
PL2
PL3
Week

Figure 9

Figure 10

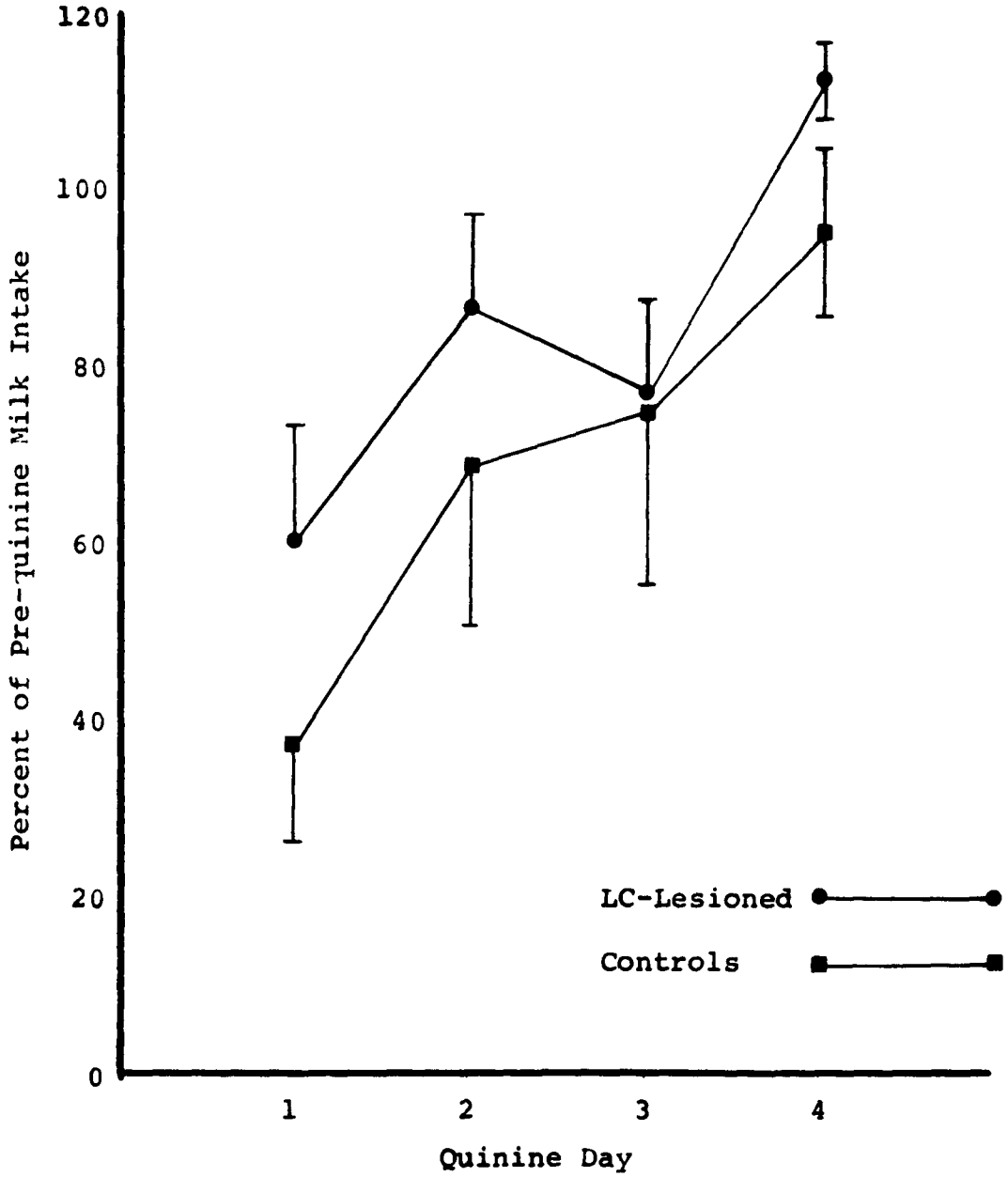

120
100
80
60
40
20
0
Percent of Pre-Quinine Milk Intake
1
2
3
4
Quinine Day
LC-Lesioned
Controls

Figure 11

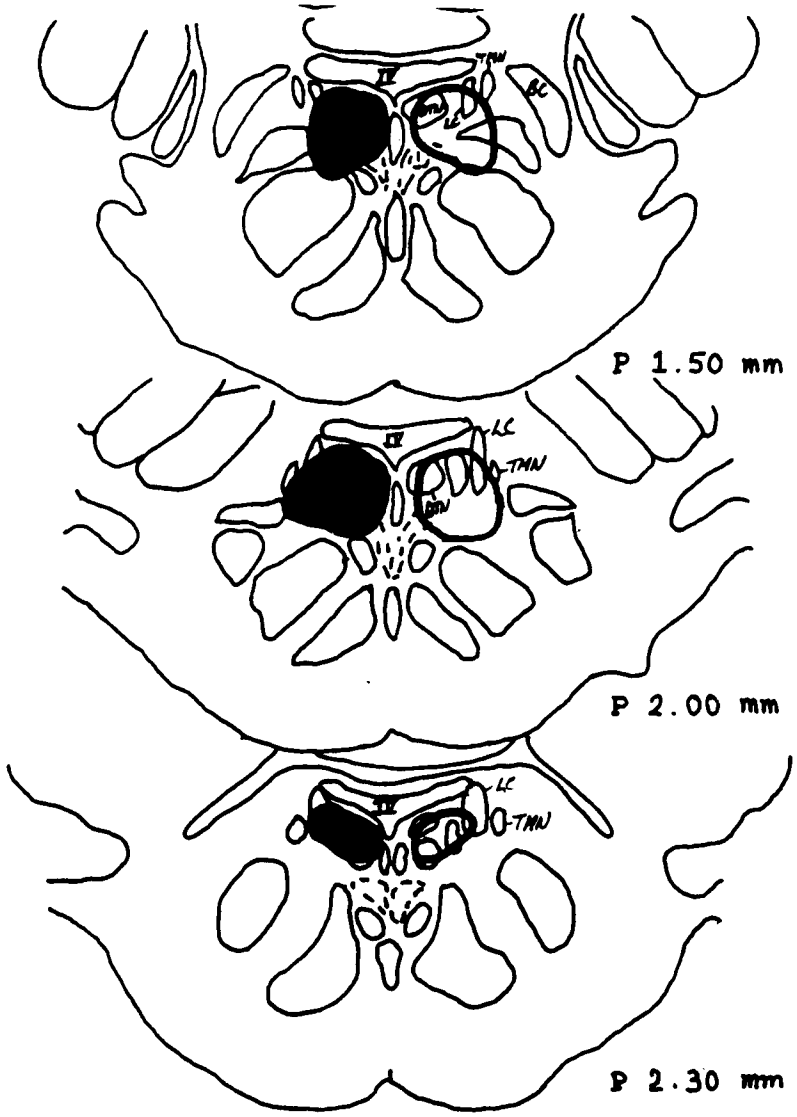
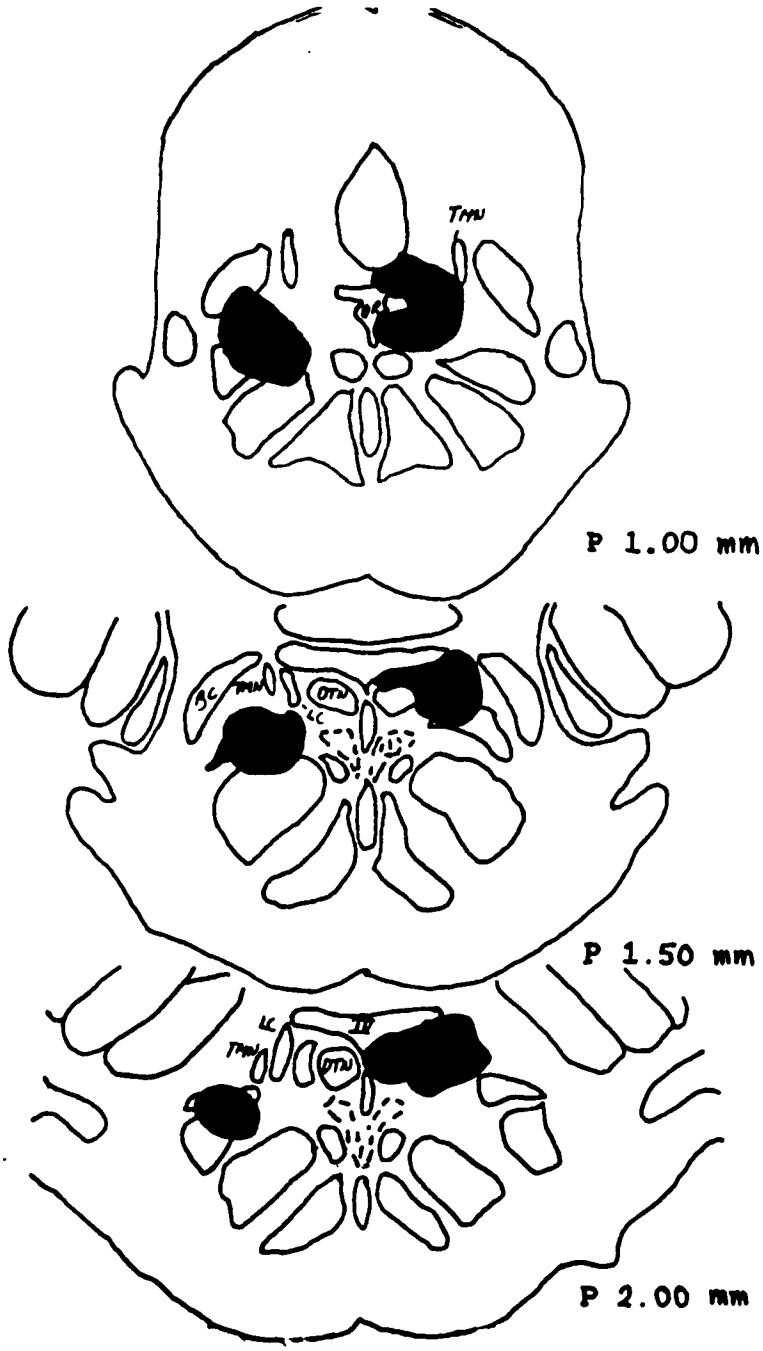


Figure 12



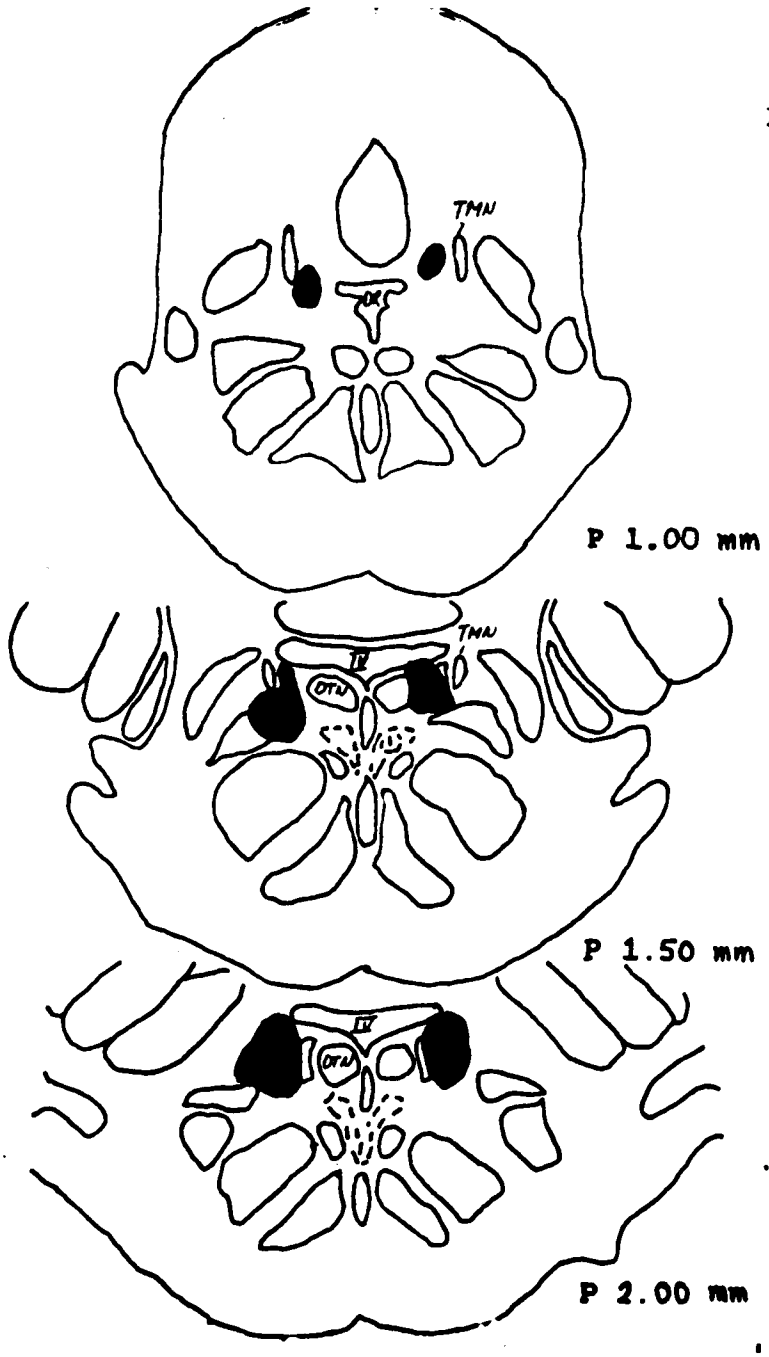


Figure 13

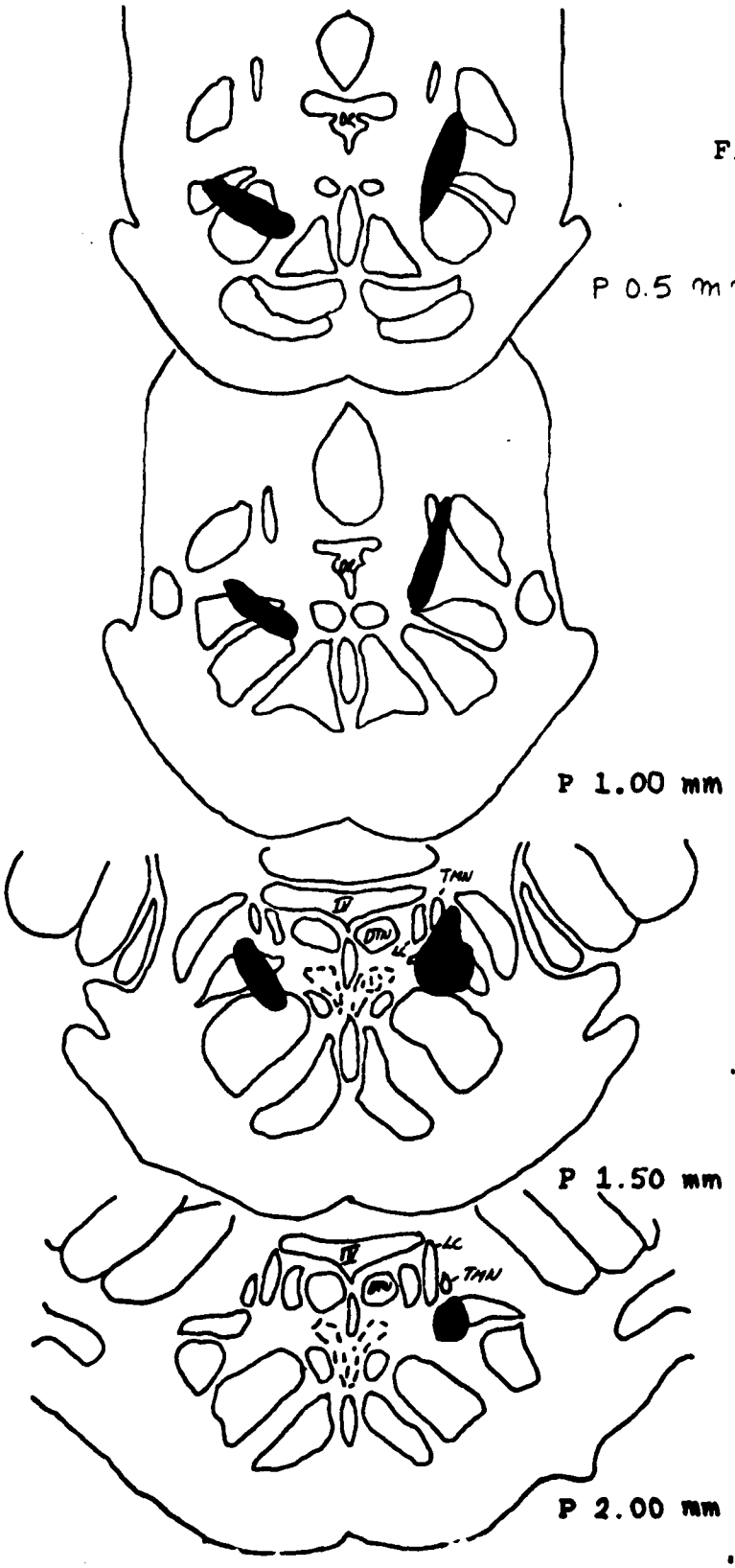


Figure 14

Figure 15

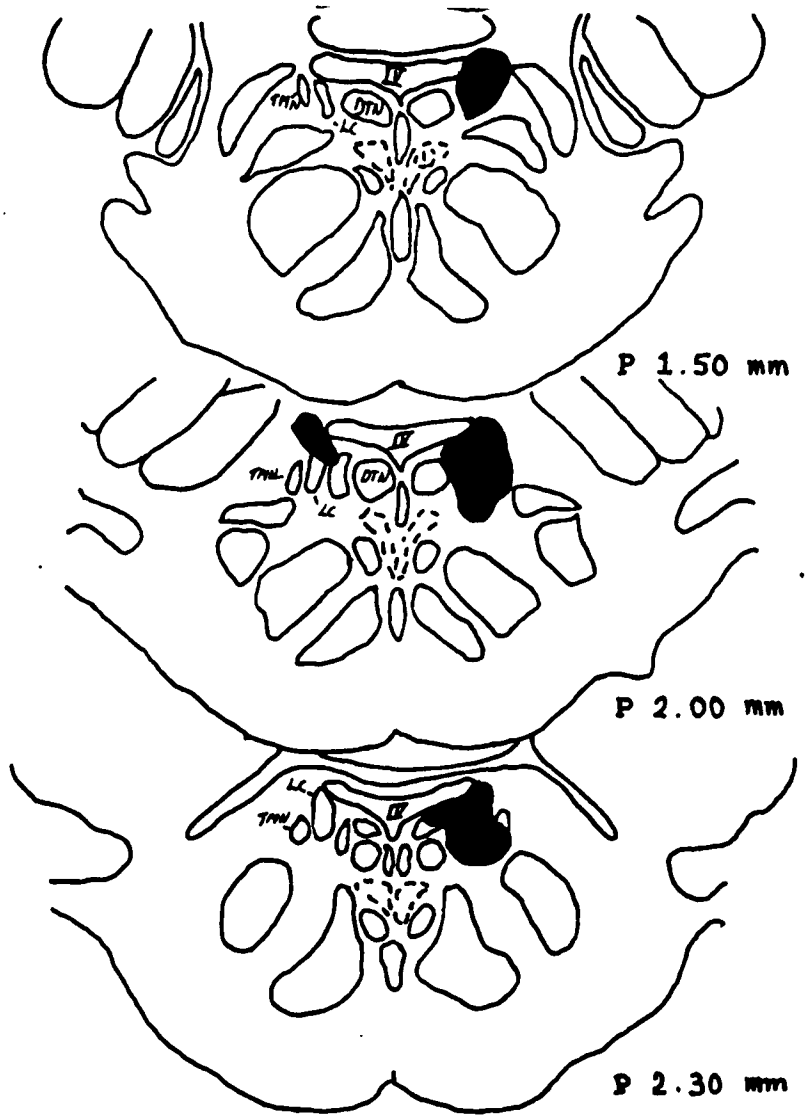


Figure 16

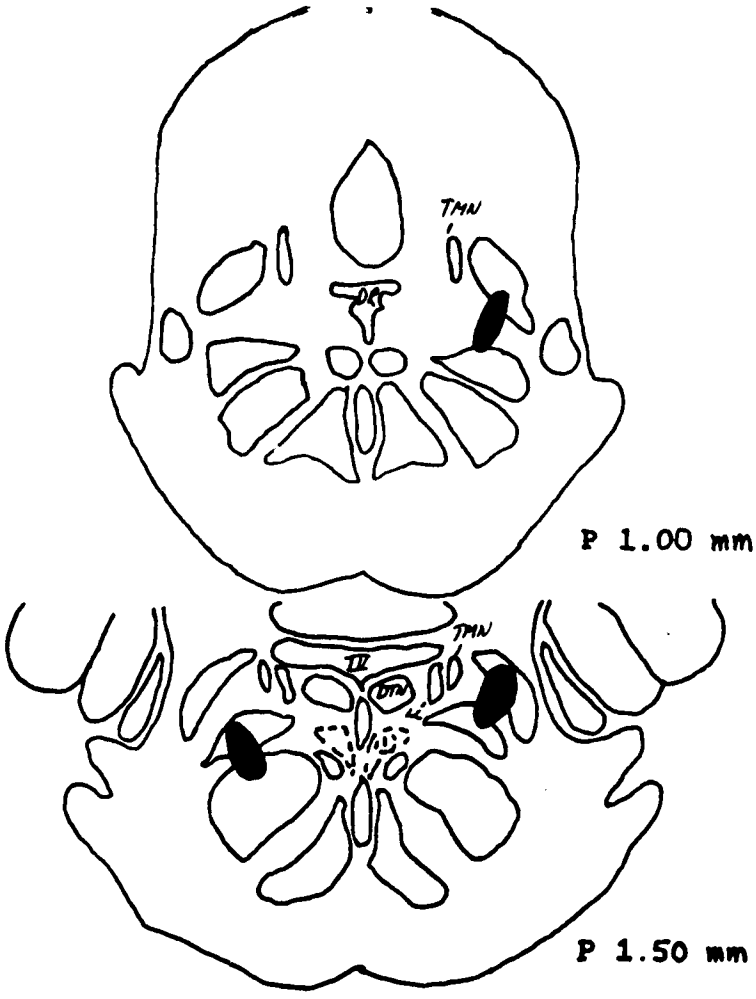


Figure 17

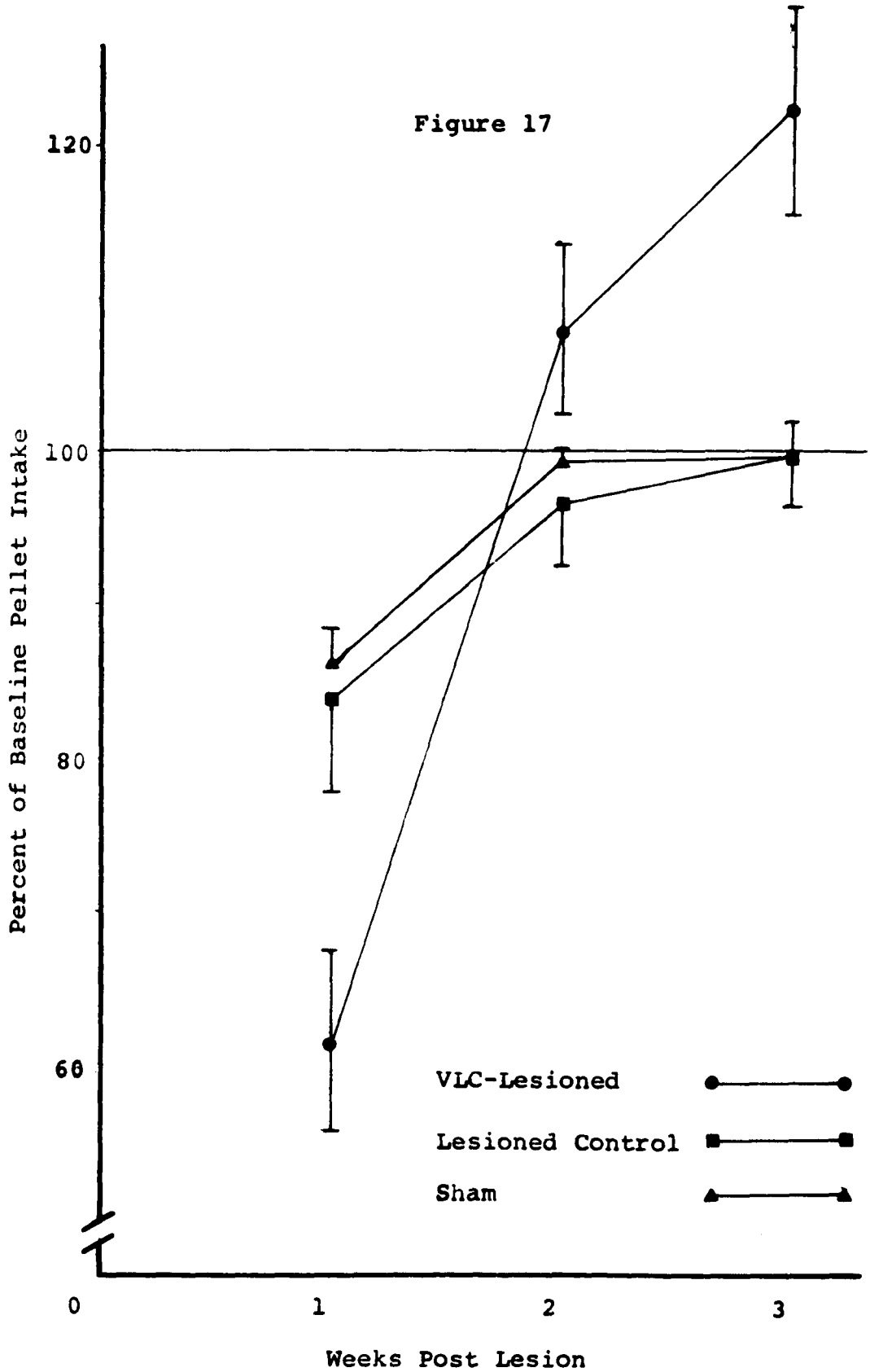

120
100
80
60
0
1
2
3
Percent of Baseline Pellet Intake
Weeks Post Lesion
VLC-Lesioned
Lesioned Control
Sham

Figure 18

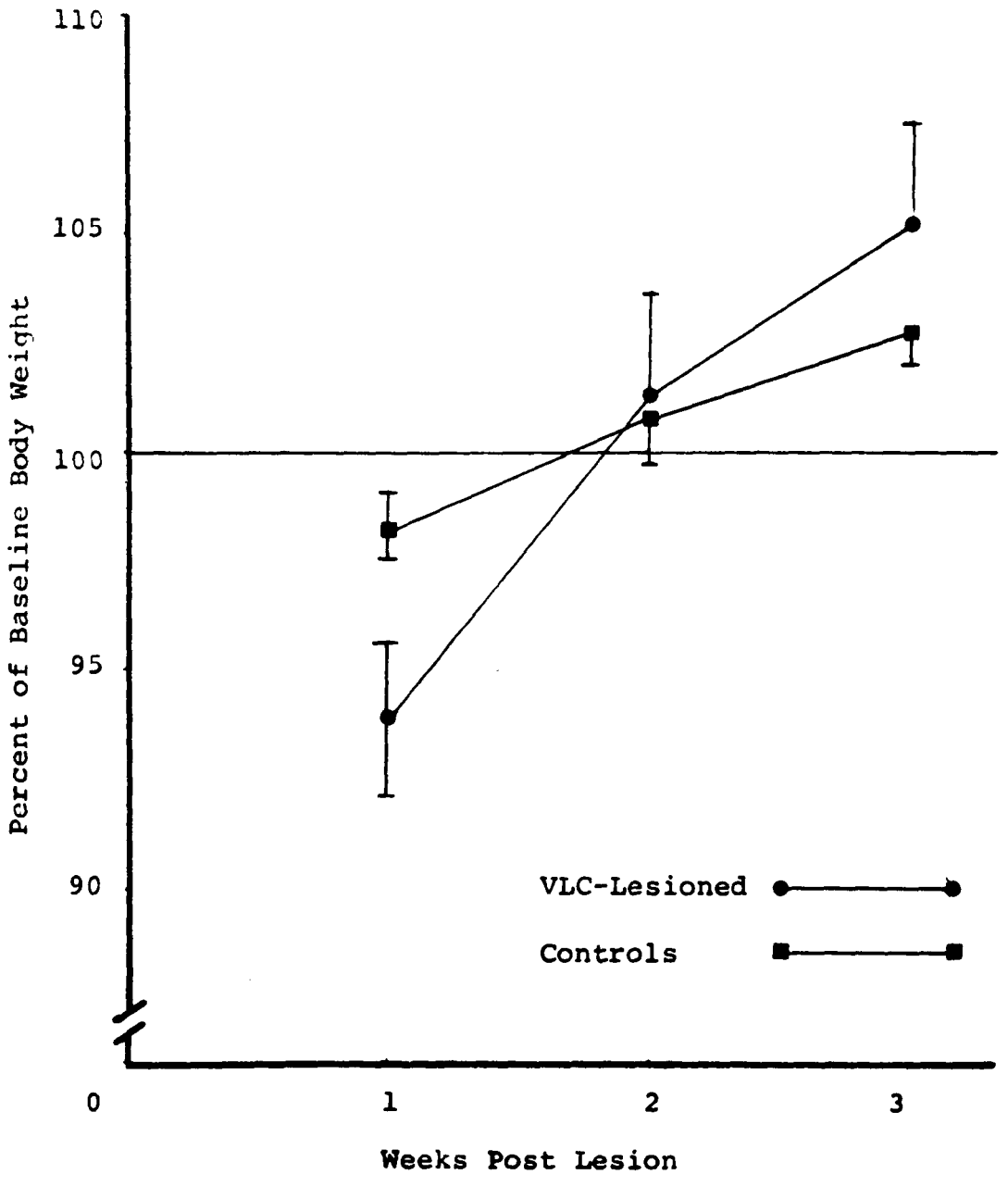
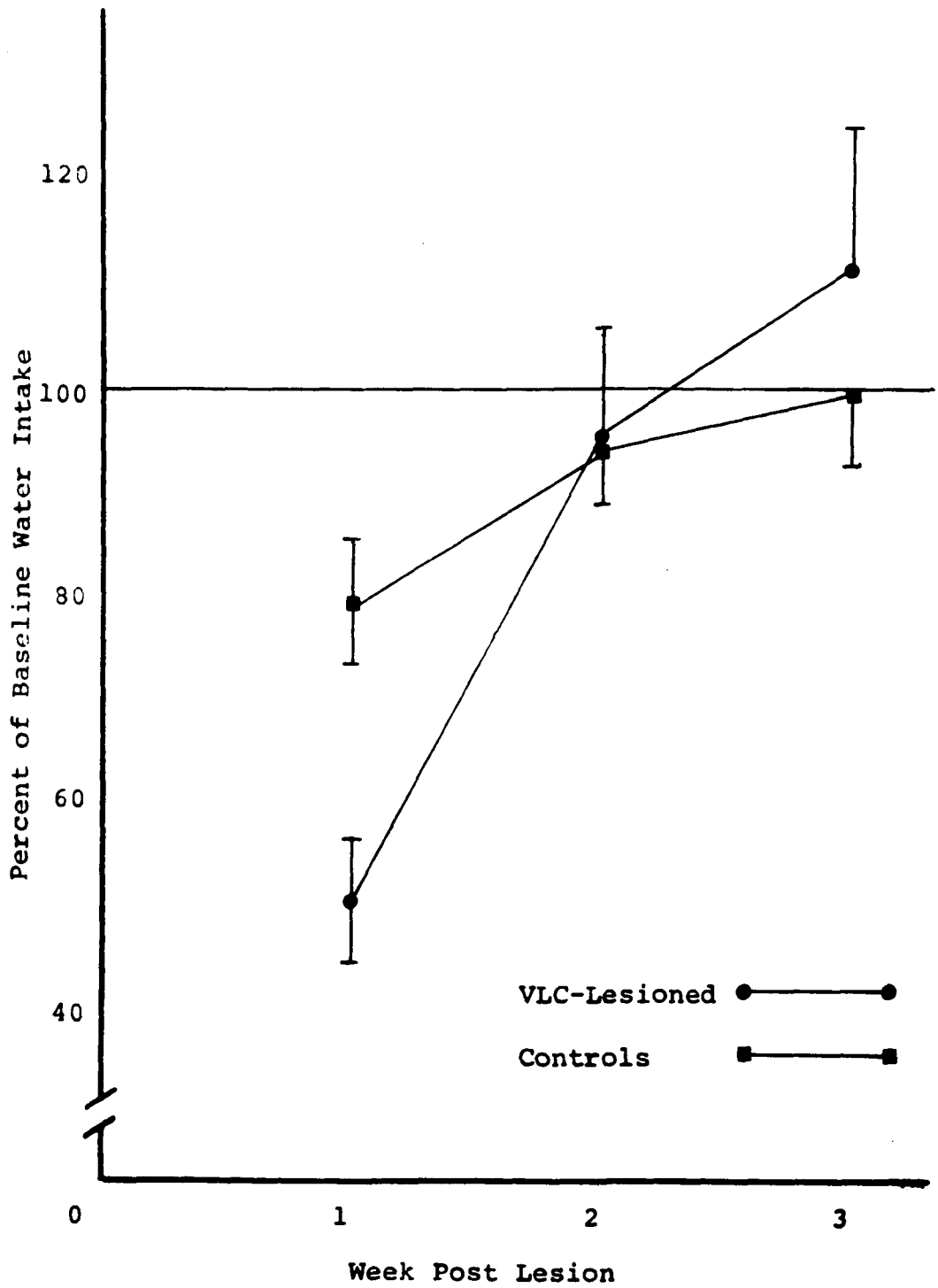

110
105
100
95
90
0
1
2
3
Percent of Baseline Body Weight
Weeks Post Lesion
VLC-Lesioned
Controls

Figure 19


120
100
80
60
40
0
1
2
3
Percent of Baseline Water Intake
Week Post Lesion
VLC-Lesioned
Controls

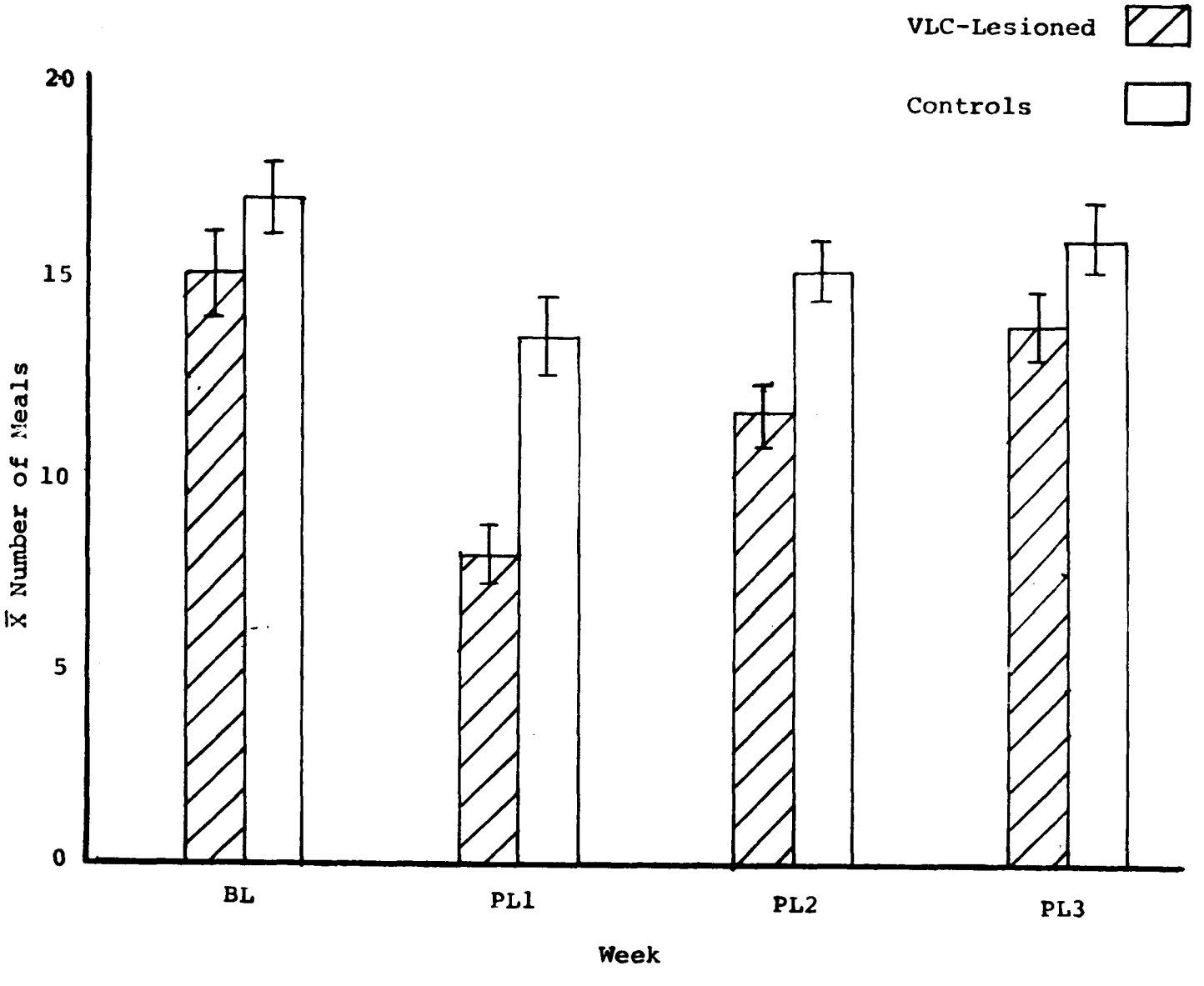

VLC-Lesioned
Controls
20
15
10
5
0
$\bar{X}$ Number of Meals
BL
PL1
PL2
PL3
Week

Figure 20

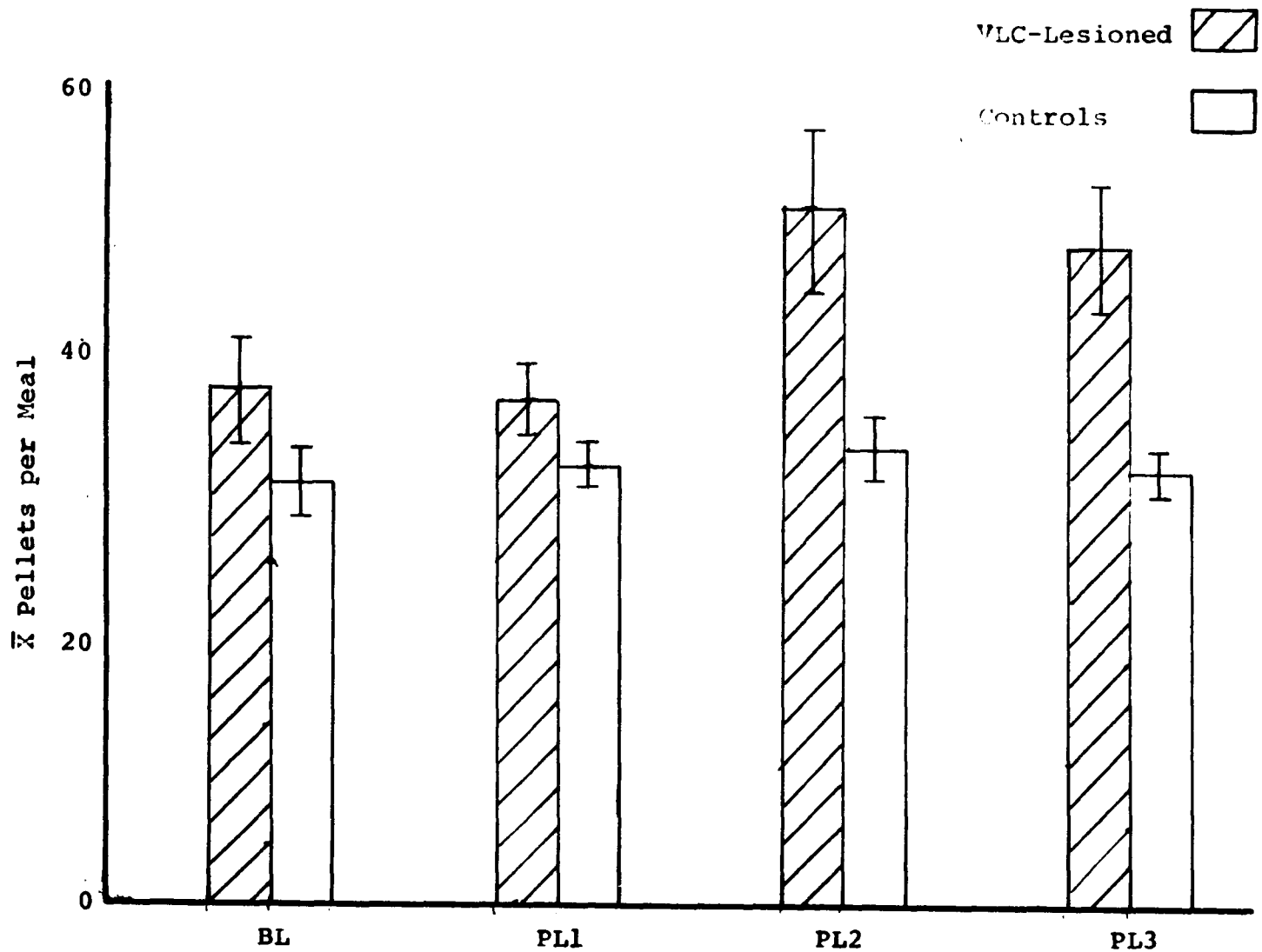

VLC-Lesioned
Controls
60
40
20
0
X̄ Pellets per Meal
BL
PL1
PL2
PL3
Week

Figure 21

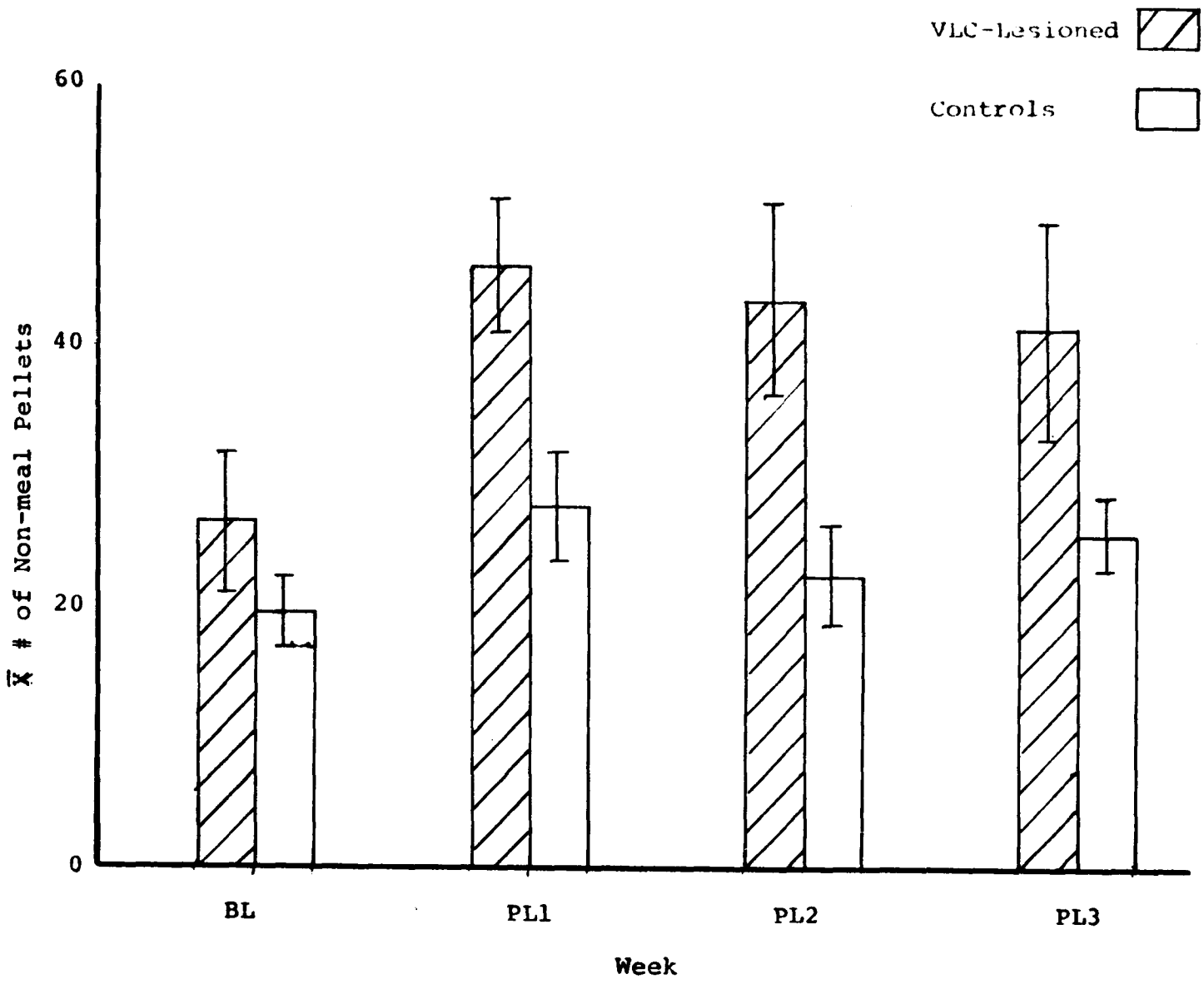

VLC-Lesioned
Controls
60
40
20
0
X # of Non-meal Pellets
BL
PL1
PL2
PL3
Week

Figure 22

Figure 23

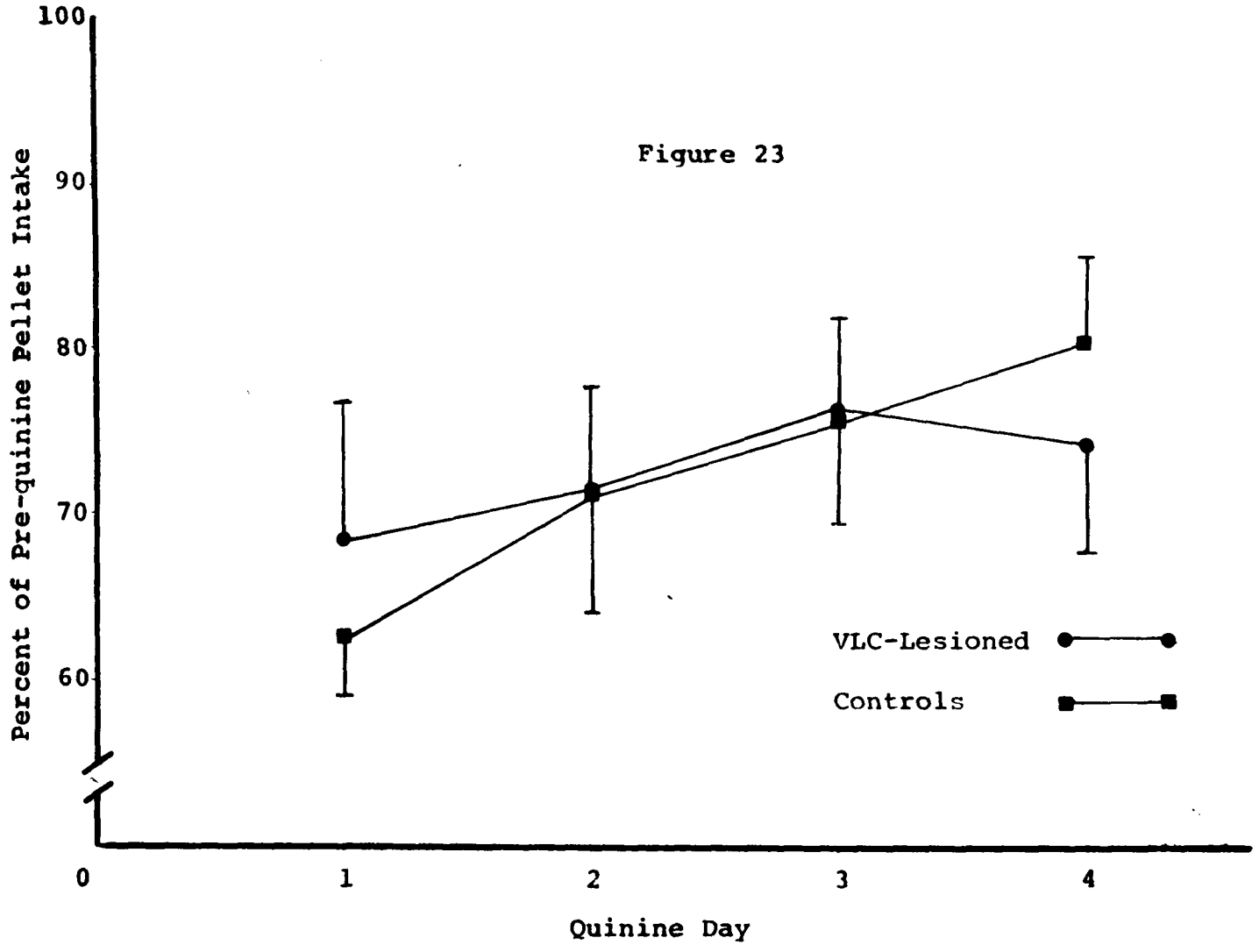

100
90
80
70
60
Percent of Pre-quinine Pellet Intake
0
1
2
3
4
Quinine Day
VLC-Lesioned
Controls

Figure 24

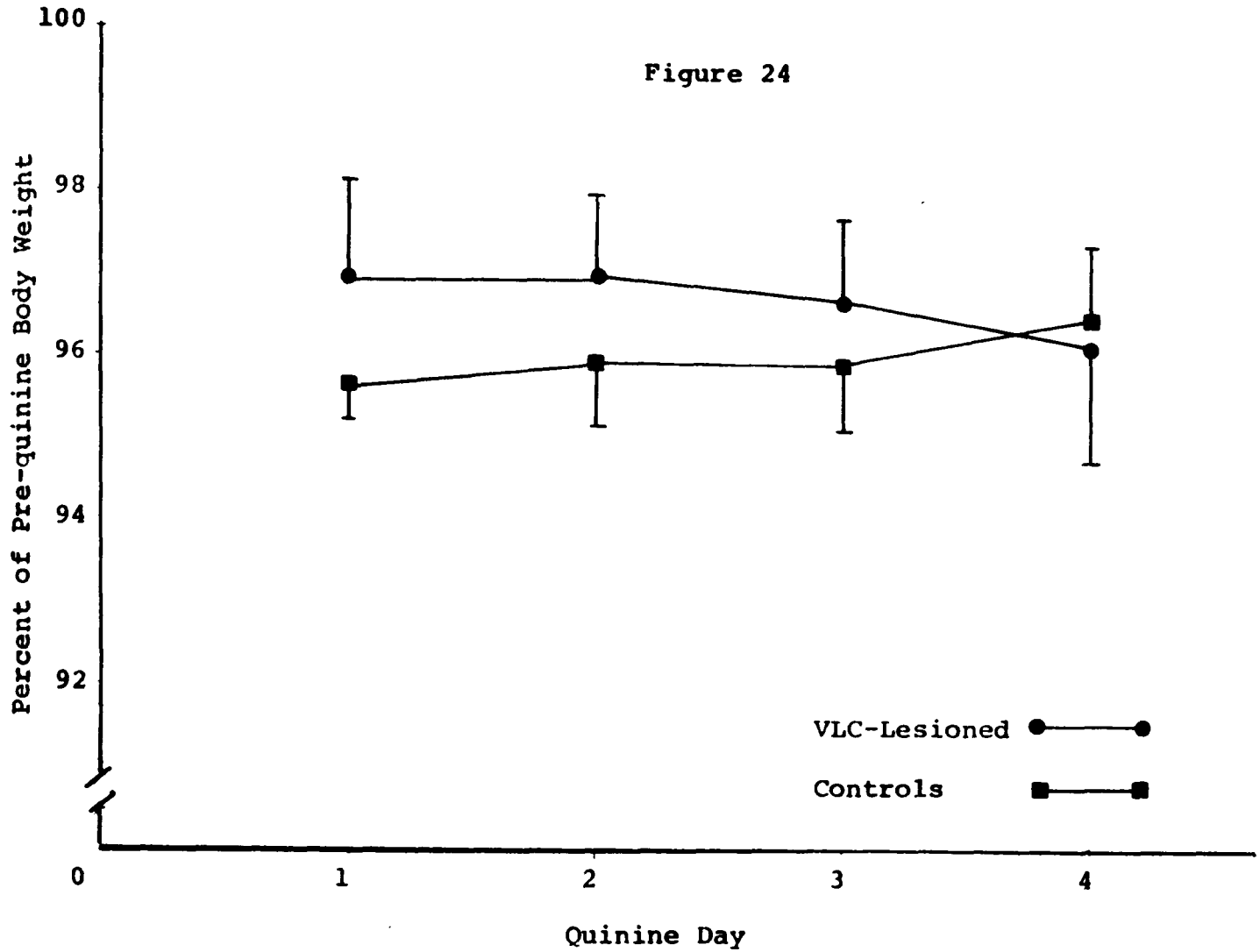

100
98
96
94
92
0
1
2
3
4
Percent of Pre-quinine Body Weight
Quinine Day
VLC-Lesioned
Controls

Figure 25