

1-1-1974

Recovery of function : some new thoughts on an old problem.

Lindy E. Harrell

University of Massachusetts Amherst

Follow this and additional works at: https://scholarworks.umass.edu/dissertations_1

Recommended Citation

Harrell, Lindy E., "Recovery of function : some new thoughts on an old problem." (1974). *Doctoral Dissertations 1896 - February 2014*. 1649.

https://scholarworks.umass.edu/dissertations_1/1649

This Open Access Dissertation is brought to you for free and open access by ScholarWorks@UMass Amherst. It has been accepted for inclusion in Doctoral Dissertations 1896 - February 2014 by an authorized administrator of ScholarWorks@UMass Amherst. For more information, please contact scholarworks@library.umass.edu.

312066011202067

RECOVERY OF FUNCTION:
SOME NEW THOUGHTS ON AN OLD PROBLEM

A Dissertation Presented

by

Lindy E. Harrell

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

DOCTOR OF PHILOSOPHY

May 1974

Major Subject: Psychology

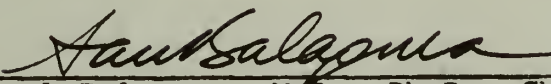
RECOVERY OF FUNCTION: SOME NEW THOUGHTS
ON AN OLD PROBLEM


A Dissertation


by

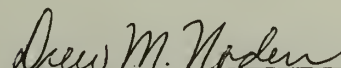
Lindy E. Harrell

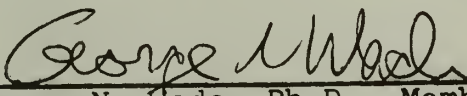
Approved as to style and content by:


Saul Balagura, M.D., Ph.D., Chairman of Committee


Richard T. Louttit, Ph.D., Head of Department


Daniel Anderson, Ph.D., Member


Drew Noden, Ph.D., Member


George N. Wade, Ph.D., Member

May, 1974

ACKNOWLEDGMENTS

I would like to extend my sincere gratitude to the members of my dissertation committee, Dr. Daniel Anderson, Dr. Drew Noden and Dr. George Wade, who added valuable insights and knowledge into my chosen area of research.

My special appreciation and thanks goes to my advisor, Dr. Saul Balagura, who through three long years guided and molded me from a naive graduate student to a person ready to assume the full responsibilities of a researcher and professor. My sincerest wishes are extended to him in his newly chosen career.

I would also like to thank the many unseen persons, who gave me moral support, aid, and knowledge during my time at this University.

ABSTRACT

Recovery of behavioral functioning following brain damage has long been known to occur. Up until this time, however, it was possible to modify the recovery period only by certain manipulations, i.e., age, multiple vs. single stage lesions, size of lesion. The experiments in this dissertation demonstrate that it is possible to modify the consequences of brain surgery without altering the above mentioned factors, by certain pre- and post-surgical treatments. Pre-surgical treatment with insulin or glucagon, five days prior to lesions of the lateral hypothalamus shortened or lengthened, respectively, the aphagic period brought about by this type of lesion. (Experiment 1). Experiment 2 demonstrated that the aphagic period following lateral hypothalamic lesions could be abbreviated by electrical stimulation in the lesioned area. In order to generalize the phenomenon, the effect of para-chlorophenylalanine pretreatment on septal rage was studied in Experiment 3. It was found that a reduction in the rage syndrome could be produced by 5-day pre-treatment with para-chlorophenylalanine, but not with 2-day pre-treatment with para-chlorophenylalanine or with 5-day pre-treatment with insulin. The final experiment examined the effects of environmental illumination on the motor impairments consequent to lateral hypothalamic

lesions. Pre-surgical darkness was found to significantly reduce motor deficits following surgery, while constant light had no effect. Post-surgical darkness, was also to some extent, able to ameliorate the motor impairments. It was postulated in all the above experiments that the pre- and post-surgical treatment modified the levels of certain neurotransmitters, which in turn, caused the alteration of the recovery period.

TABLE OF CONTENTS

	Page
ACKNOWLEDGMENTS	ii
ABSTRACT	iii
TABLE OF CONTENTS	v
LIST OF FIGURES	vi
INTRODUCTION	1
EXPERIMENT 1: The Modulation of the Recovery Period after Lateral Hypothalamic Lesions by the Glucodynamic Hormones	9
Methods	10
Results	12
Discussion	15
EXPERIMENT 2: Acceleration of Functional Recovery Following Lateral Hypothalamic Damage by Means of Electrical Stimulation in the Lesioned Areas.	18
Methods	18
Results	20
Discussion	21
EXPERIMENT 3: The Generalization of a Phenomenon: The Effect of Para-chlorophenylalanine on Septal Rage	24
Methods	24
Results	26
Discussion	29
EXPERIMENT 4: The Effects of Dark and Light on the Recovery Period Following Diencephalic Lesions.	34
Methods	35
Results	37
Discussion	41
GENERAL DISCUSSION	45
REFERENCES	48

LIST OF FIGURES

Figure	Page
1. The influence of injections of insulin, glucagon, and saline on the recovery of feeding after lateral hypothalamic lesions. Each data point indicates a group mean for 1 day	14
2. Coronal sections passing through the midhypothalamus of rats treated with saline (top), insulin (middle), or glucagon (bottom) before surgery. In every case the lesion encompassed the lateral hypothalamus, the inner edge of the internal capsule, and the ventral aspect of the fields of Forel	16
3. Histology of a typical control (upper) and experimental (lower) animals showing the casts left by the electrodes.	22
4. Subjective ratings of rage and habituation to poke following septal lesions. <u>First row</u> : The effect of 5 days of Insulin pre-treatment. <u>Second row</u> : The effect of 2 days PCPA pre-treatment. <u>Third row</u> : The effect of 5 days PCPA pre-treatment.	28
5. Diagrammatic representation of the lesion placements. Black area = minimum extent of lesion. Striped area = maximum extent of lesion.	30
6. Latencies to execute motor tasks before and after surgery. <u>First row</u> : Illustration of motor tasks (arrows indicate type of response expected). <u>Second row</u> : Effects of lateral hypothalamic lesions in rats kept on a 12 hour light-dark cycle (C_d = lesioned during dark, C_l = lesioned during light). <u>Third row</u> : Effects of lateral hypothalamic lesions in animals maintained in constant dark (D-D) and light (L-L) before and after surgery. <u>Fourth row</u> : Effects of lateral hypothalamic lesions in rats kept in constant dark before, but shifted to constant light after surgery (D-L), and vice versa (L-D).	40

Figure	Page
7. Histology from representative animals in each group. Lesions in all animals encompassed the lateral hypothalamus, the medial edge of the internal capsule and the ventral aspects of the fields of Forel.	42

INTRODUCTION

* Recovery of behavioral function following brain damage has frequently been observed in both animals and man. Thus eating behavior gradually returns to the lateral hypothalamic lesioned animal, while man is able to regain many motor and sensory functions which may be lost due to cerebral vascular accidents. *At the present time, however, the compensatory mechanisms which underlie recovery have not been clearly identified. One possible explanation of this phenomenon might be regeneration. * In the adult nervous system, however, there is no evidence that nerve cells may be capable of division, growth and differentiation. * Following destruction of nerve fibers, non-neural elements proliferate and migrate into the region of damage, disposing of the wrecked fibers and replacing them with impenetrable scar tissue. Thus, even if the cell bodies are intact after brain damage, the possibility of regeneration within the central nervous system is doubtful.

* To contend with this fact and with that of behavioral recovery following brain damage, several hypotheses have been presented, most centered on a reorganization of neural circuits. Lashley (1963) thought that compensation or vicarious function might be due to overlapping neuronal fields such that specific memory traces are

scattered over a large area of the brain. Kennard (1938) suggested that other structures may take over the function of the tissue that has been removed. However, neither of these theories have been able to specify the particular pathways or mechanisms involved in the recovery of function. * More recently, evidence has started to appear suggesting that collateral sprouting inside the central nervous system may be responsible for recovery (Raisman, 1969; Wall and Egger, 1971). * In this case, heterotypical re-innervation occurs as the result of the formation of new contacts by persisting intact fibers in the de-afferented area. Clearly, if the re-innervation were of this type, partial loss of specificity would occur. Behaviorally, this has been clearly demonstrated. * For example, animals recovered from lateral hypothalamic lesions do eat; however, they show many other types of regulatory deficits, i.e., prandial drinking, failure to eat following induced hypoglycemia, failure to drink following osmotic stress (Epstein and Teitelbaum, 1964; Epstein and Teitelbaum, 1967). * At the present time, however, no adequate theory has been presented to explain the alterations in the central nervous system which underlie recovery of function in the adult mammal.

* There exists, however, a growing body of experimental

evidence in support of the notion that central nervous system injury occurring early in life ultimately produces less behavioral dysfunction than does comparable injury sustained at later ages. Behaviors shown to be spared following such early occurring lesions have included: somato-motor function (Kennard, 1936, 1938, 1942), visual patterning and frequency discrimination (Dory, 1961; Tucker and Kling, 1966; Wetzel, Thompson, Horel, and Meyer, 1965), auditory duration discrimination (Benjamin and Thompson, 1965), object discrimination (Raisler and Harlow, 1965), maze learning (Tsang, 1937), affective-vegetative (Kling, 1962) and maternal behavior (Beach, 1938). It is possible that the sparing effect that one observes after brain damage in the infant is due to a process of neural reorganization subsequent to early injury, such that other central nervous system areas are able to subsume the functions which have temporarily been lost through injury. * This reorganization might be viewed as some intrinsic compensatory mechanisms of the immature central nervous system which is unavailable to the fully matured brain.

Recently, it has been suggested that the recovery of function in the adult animal parallels the encephalization functions observed in the infant. Recovery of food and water intake following lateral hypothalamic

damage in the adult rat is known to progress through four distinct phases: aphagia and adipsia, anorexia and adipsia, dehydration-aphagia and adipsia, and recovery of food and water intake (Teitelbaum and Epstein, 1962). These same four stages may be observed in infant rats whose development has been retarded due to starvation or thyroidectomy (Teitelbaum, Cheng, and Rozin, 1969; Cheng, Rozin, and Teitelbaum, 1971). Thus recovery from lateral hypothalamic damage in the adult rat and the stages of development of the control of food and water intake in the infant have been found to be parallel. Further support for the encephalization of behavior after brain damage in the adult comes from the work of Hines (1942). A comparison between adult cortical damaged rhesus monkeys and normal developing infants revealed the existence of stages in normal developing motor systems which closely resembled the recovery of motor function after adult brain damage. Thus, developing infant monkeys demonstrated symptoms of motor damage, such as forced grasping, spasticity and extensor rigidity, which are common after cortical damage in the adult.

* In the clinical literature it is evident that many of the infantile reflexive patterns of approach and withdrawal appear after cortical damage in the adult (Denny-Brown, 1958; Denny-Brown and Chambers, 1958). Thus

stroking the palm of the hand will elicit voluntary grasping, deep pressure in the palm will elicit strong maintained flexion of the fingers, a light stroking movement of the skin will elicit closure of the fingers around the stimulus object, etc. *It is interesting to note that the recovery of voluntary control of the hand after frontal lobe damage in the adult parallels the development of such voluntary control in the infant, i.e., control by local contact reflexes, to control by more tenuous and distant stimuli with projection into space, to eventual control of reaching and grasping (Teitelbaum, 1967). *Thus the recovery of some functions seen in the adult animal after brain damage may mirror the original sequence followed by the animal's nervous system in its development. *Obviously, this still does not account for the mechanisms which underlie recovery of function, but in the future it may well shed some light on the process that is occurring after central nervous system damage.

While recovery of function after infant brain damage has been noted previously, recent investigation suggests that such recovery is also possible in mature organisms. *Thus multiple-stage lesions produce less task deficiency than single stage ablations of identical tissue. Chow and Randall (1964) demonstrated that multiple-stage removal of the reticular formation in cats lead to the

normal learning of both appetitive (black-white discrimination for food) and aversive (shuttle box) tasks, while single stage lesions of this area produce large task impairments. Since then Stein, Rosen, Graziadier, Miskin and Brink (1966) have shown that two stage lesions of the amygdala, hippocampus, and frontal cortex in rats produce no learning deficits on a number of tasks, i.e., dark-light discrimination plus reversal, acquisition of delayed spatial alteration, acquisition of non-spatial, simultaneous visual discrimination. These ameliorating effects of serial lesions on learning tasks have also been demonstrated in monkeys after ablation of primary cortex (Steward and Ades, 1952) and after damage to the association cortices (Rosen, Stein and Butters, 1971).

* This suggests that the apparently normal behavior of the multiple-stage lesioned animals must be due to some naturally occurring reorganization of the activity of the central nervous system.

Modification of the recovery period following brain lesions has also been found to occur following certain pre- and post-surgical manipulations. * Thus maintaining animals at reduced body weight prior to lateral hypothalamic lesioning has been found to shorten the recovery period (Powley and Keesey, 1970; Harrell and Balagura, 1974). Conversely, obesity prior to lesioning will

lengthen it (Balagura and Harrell, 1974). Alteration of the recovery period following lateral hypothalamic lesions has also been found to occur by modifying the brain levels of the neurotransmitter norepinephrine, which has been hypothesized to mediate feeding behavior (Grossman, 1960). Hence, it has been found that the implantation of norepinephrine into the lateral hypothalamus following destruction of this area leads to the reversal of the aphagia (Berger, Wise and Stein, 1971).

* More recently, it has been demonstrated that systemic injections of α -methyl-p-tyrosine, which blocks the production of norepinephrine, three days prior to placement of lateral hypothalamic lesions shortened the length of the recovery period, perhaps as a result of denervation supersensitivity (Glick, Greenstein and Zimmerberg, 1972).

* The recovery period following lateral hypothalamic lesions has also been shortened by the intraventricular injection of nerve growth factor immediately following lesioning.

* It was hypothesized that nerve growth factor may influence the recovery period in one of two ways: a denervation supersensitivity or by causing an enhanced fiber growth (Berger, Wise and Stein, 1973).

Some of the above mentioned studies suggest that the behavioral effects of brain damage may be ameliorated by modification of the central nervous system either directly

or indirectly, before brain lesioning. *The present research was designed to investigate some of the variables which might influence the central nervous system in such a way as to reduce or increase behavioral dysfunctioning following iatrogenic brain damage. The consequences of this research may in the future have far-reaching effects into the field of neurosurgery and into the treatment of brain damaged individuals.

EXPERIMENT 1

The Modulation of the Recovery Period
after Lateral Hypothalamic Lesions
by the Glucodynamic Hormones

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

For quite sometime, it was assumed that this recovery

period was unmodifiable. Recently, however, it was found that maintaining animals at reduced body weight prior to lateral hypothalamic lesions shortens the recovery period (Powley and Keesey, 1970; Harrell and Balagura, 1974; Balagura and Harrell, 1974). It was postulated that lesions of the lateral hypothalamus result in a lowering of the set-point for weight regulation and that the normal interruption of feeding following such lesions is the consequence of an effort by the animal to bring its body weight into balance with this new level of regulation. If this is the case, then obesity should lengthen the recovery period. In fact obesity produced by insulin and progesterone treatment in rats prior to lateral hypothalamic lesioning produces a lengthening of the recovery period (Balagura and Harrell, 1974).

Since insulin and glucagon are intimately related to food intake (MacKay, Calloway and Barnes, 1940; Salter, 1960), the present study investigated the effects of pre-treating animals with these two hormones on the recovery period following lateral hypothalamic lesioning.

Method

Subjects:

Twenty-one male Holtzman albino rats weighing between 360-380 grams were housed individually in a temperature controlled room ($72^{\circ}\text{F} \pm 2^{\circ}$). Illumination was provided

by standard fluorescent ceiling lights (on at 0600, off at 1800).

Adaptation and Experimental Procedure:

To permit the rats to adapt to the colony and to obtain information on individual body weight and food intake, the rats were given three weeks of adaptation with Purina rat chow ad libitum. Food intake and body weight were recorded daily throughout the experiment. For five days prior to surgery, seven of the rats were given 0.2 ml subcutaneous injections of glucagon (0.1 ml at 0000, 0600, 1200, and 1800 hours); seven were injected with 0.2 ml of Semilente insulin (3 units at 0000 and 1200 hours and mock injections at 0600 and 1800 hours); the remaining seven were injected with 0.2 ml of isotonic saline (at 0000, 0600, 1200, and 1800 hours). In order to maintain body weight during the hormone treatment period, the rats were fed an amount equal to the average amount consumed during the preceding five days. The injections were discontinued 24 hours before surgery.

Lateral hypothalamic lesions were made under Nembutal anesthesia (50 mg/kg) with the aid of a stereotaxic instrument. Direct anodal current of 1 ma was delivered for 20 seconds through an Insulex-coated stainless steel electrode (0.2 mm in diameter) exposed 0.5 mm at the tip. The stereotaxic coordinates with the skull flat between

bregma and lambda were: 5.6 anterior to the interaural line, 2.0 mm lateral to the midsagittal sinus, and 7.7 mm below the dorsal surface of the cortex. The rats were returned to their cages after surgery and their feeding behavior observed. If an animal had not recovered eating behavior within 7 days, intragastric feeding of milk (5 ml, three times daily) was begun. After the recovery of eating behavior, which in this case was defined as the consumption within a 24 hour period of 3 or more grams of Purina chow, the animals were killed and their brains removed, sliced in sections $60\mu\text{m}$ thick, and stained with cresylecht violet for histological verification of the lesion placement.

Results

Figure 1 summarizes the results. During the hormone treatment each animal maintained its preinjection body weight. After lateral hypothalamic lesions, the animals that had received saline injections showed the characteristic aphagia and recovered from it in an average of 3.8 ± 2.7 (SEM) days. Prior insulin treatment shortened the recovery period to 1.4 ± 1.6 days. Prior glucagon treatment lengthened the recovery period to 6.6 ± 3.1 days. The recovery periods after insulin and glucagon treatments differed significantly in length from those of the saline

controls ($p < 0.05$; two-tailed t-test, $df = 12$). An analysis of variance revealed that postsurgical food intake, compared to that of the saline group, was increased by prior insulin treatment and decreased by prior glucagon treatment ($F(2,18) = 15.3$, $p < 0.001$). The analysis also showed an across-days effect ($F(9, 162) = 2.5$, $p < 0.01$), indicating that the groups reached an eating plateau at different times after the lesion -- the insulin group first, the saline group next, and the glucagon group last. The behavior observed during the immediate post-surgical period was the result of the interaction of hormone treatment and the lateral hypothalamic lesions, since hormone administration per se does not cause aphagia (Balagura, 1968; Holloway and Stevenson, 1964).

The effect of prior hormone treatment on post-lateral hypothalamic lesioned animal's body weight paralleled the feeding effect. Body weight differed across groups $F(2, 18) = 13.2$, $p < 0.001$ and across days ($F(9, 162) = 4.5$, $p < 0.001$).

★ In every case our lesions encompassed bilaterally the area of the lateral hypothalamus and the medial fore-brain bundle, as well as the most medial edge of the internal capsule at the level of the ventromedial hypothalamus. Thus the results obtained were caused by the

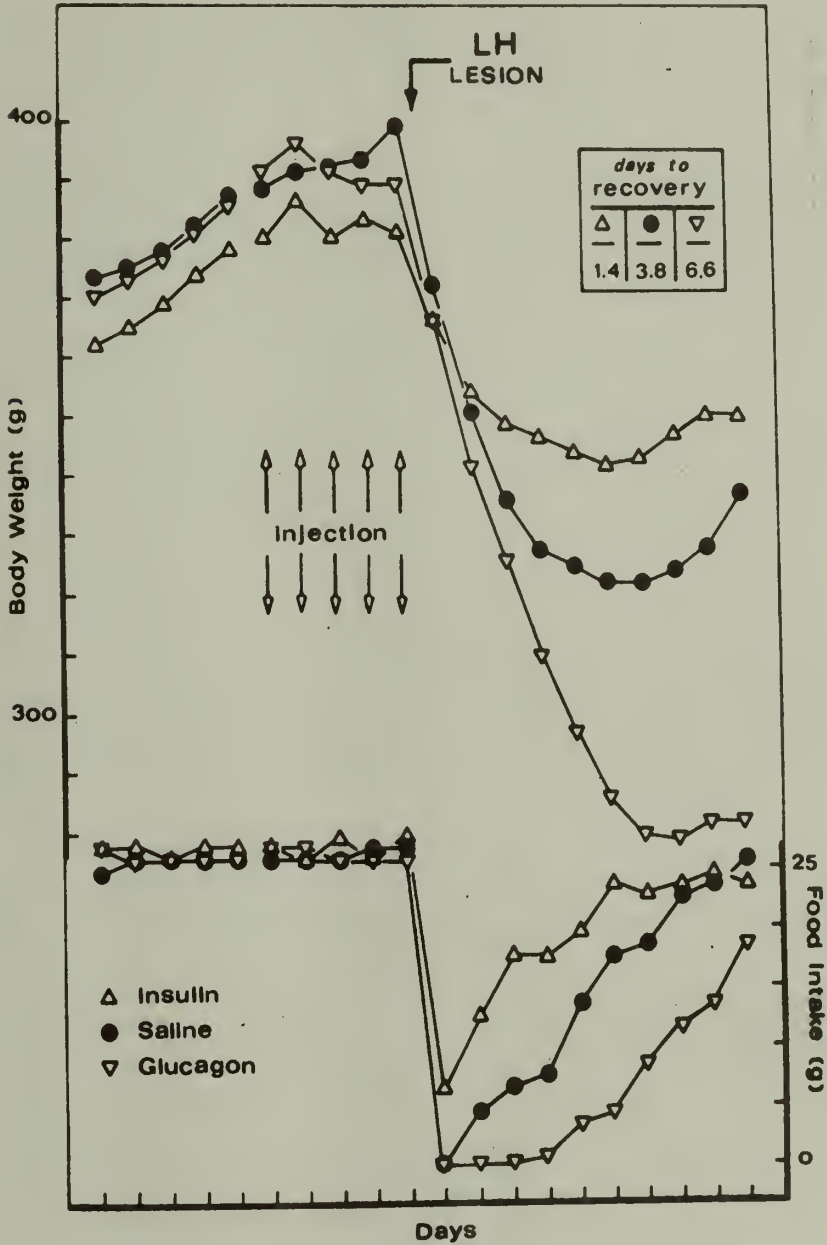


Figure 1. The influence of injections of insulin, glucagon, and saline on the recovery of feeding after lateral hypothalamic lesions. Each data point indicates a group mean for 1 day.

hormone treatment rather than by differences in the brain lesions. Histological examination of coronal sections revealed no major differences among groups (Figure 2). The top section of Figure 2 was taken from a saline-treated animal that recovered eating behavior in 3 days. The middle and bottom sections of Figure 2 are essentially indistinguishable; the middle is from an insulin-treated animal with less than 1 day of aphagia, and the bottom is from a glucagon-treated animal with 6 days of aphagia.

Discussion

It has been hypothesized that the shortening of the lateral hypothalamic recovery period produced by body weight reduction before surgery is due to a shift in a regulatory set point for body weight (Powley and Keese, 1970). However, this study demonstrates this phenomenon without altering body weight or food intake before surgery. The effect of the two glucodynamic hormones on the recovery period could indirectly be caused by their action on glucose utilization (Turner and Bagnara, 1971) or could be caused by their effects on neurotransmitters.

Reduction of brain norepinephrine by systemic injection of α -methyl-p-tyrosine 3 days before lateral hypothalamic lesions reduces the recovery period (Glick, Greenstein and Zimmerberg, 1972), probably as a result of denervation supersensitivity. Norepinephrine has been

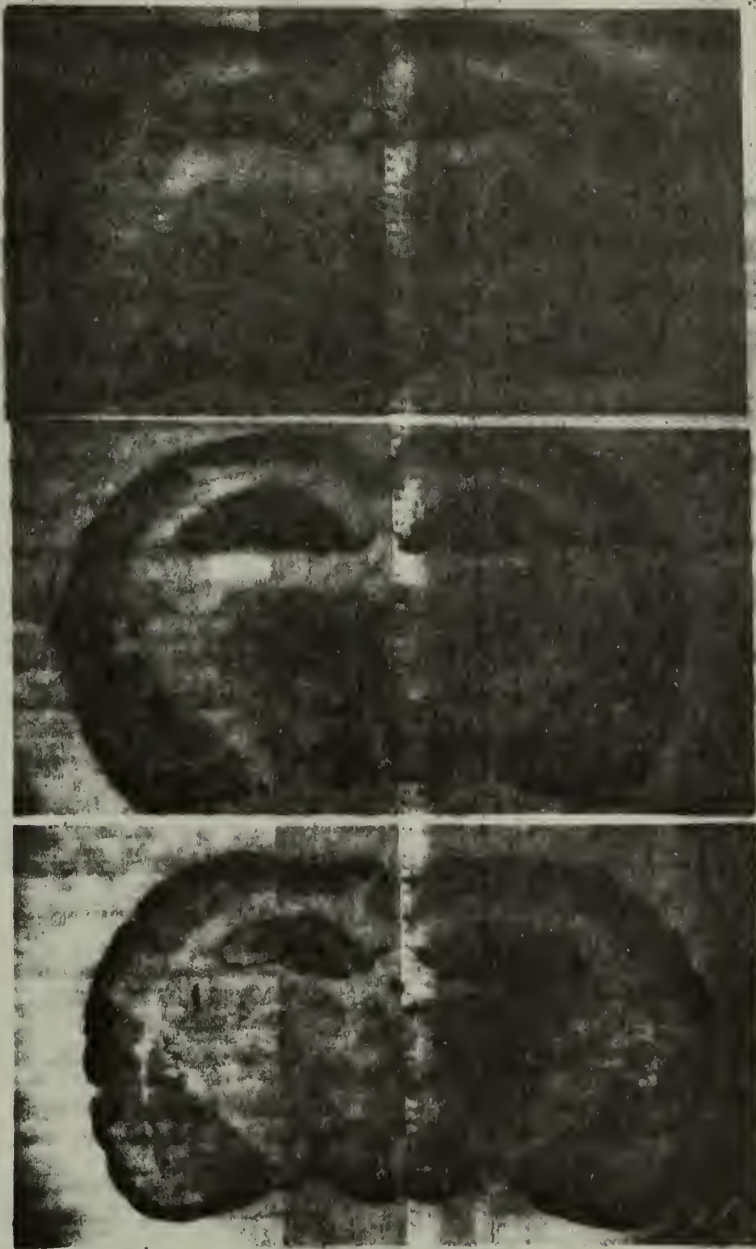


Figure 2. Coronal sections passing through the midhypothalamus of rats treated with saline (top), insulin (middle), or glucagon (bottom) before surgery. In every case the lesion encompassed the lateral hypothalamus, the inner edge of the internal capsule, and the ventral aspect of the fields of Forel.

hypothesized to be the neurotransmitter in the neural mediation of feeding behavior (Grossman, 1960). Little is known of the effects of glucagon on the central nervous system. Insulin, however, has been shown to increase the levels of both tyrosine hydroxylase and dopamine β -hydroxylase (Weiner and Mosimann, 1970; Viveros, Arqueros, Connet, Kirschner, 1969), which are important enzymes in the conversion of tyrosine to norepinephrine. Perhaps, presurgical treatment with insulin, as with α -methyl-p-tyrosine, produces denervation supersensitivity in the norepinephrine neural system. Glucagon may also influence the norepinephrine system, but even less is known of its mode of action. However, insulin and glucagon may be influencing the postsurgical recovery in an entirely different manner.

Regardless of the mechanism by which insulin and glucagon alter the recovery period, basically identical lesions to the same brain area in the present experiment led to three quantitatively different recovery periods. This type of phenomenon may underlie the recovery of function after damage to other parts of the central nervous system.

EXPERIMENT 2

Acceleration of Functional Recovery Following
Lateral Hypothalamic damage by Means of Electrical
Stimulation in the Lesioned Areas

In the first experiment, I was able to abbreviate or lengthen the aphagic period which is consequent to lesions of the lateral hypothalamus. It was postulated that this was due to the interference with norepinephrine metabolism. Recently, it has been found that electrical stimulation of the medial forebrain bundle at the level of the lateral hypothalamus leads to a release of norepinephrine (Stein and Wise, 1969). Taken together, these facts would predict that the recovery of feeding following lesions of the lateral hypothalamus would be shortened by electrical stimulation of the neural tissue neighboring the lesions. The present experiment was performed to test this hypothesis.

Method

Subjects:

The experimental animals were ten Holtzman, albino male rats. The rats were housed individually and were fed ad libitum on Purina Laboratory pellets placed on the floor inside the cage. Food consumption was measured daily. Food spillage was collected daily from paper

placed underneath the cages, and was taken into account in calculating food intake. Illumination was provided by standard fluorescent ceiling lights (on at 0600, off at 1800).

Electrode Implantation:

The electrodes were No. 3 insect pins (0.9 mm in diameter) coated with insulex except for 0.5 mm at the tip. It has been found that this size electrode produces a mechanical lesion and easily detectable neurological signs (aphagia) when implanted into the lateral hypothalamus. The stereotaxic coordinates which were employed in placing the electrodes in the lateral hypothalamus (skull horizontal between bregma and lambdoid) were: 7.0 mm anterior to the interaural line, 2.0 mm lateral to the midsagittal sinus, and 7.8 mm below the surface of the cortex. A wire around one of the screws that was used to secure the electrodes to the skull was used as the reference ground for the two electrodes.

Procedure:

On the day following hypothalamic implantation of the macroelectrodes, ten animals that were found to be aphagic were randomly divided into two groups: control and experimental. The experimental animals received one hour of bilateral, lateral hypothalamic stimulation daily

until eating behavior was reinstated. The control animals received no electrical stimulation. Stimulation through the electrodes consisted of a train of biphasic pulses 1.0 msec in duration at a rate of 100 Hz. Current intensities were held constant for each experimental animal at 0.008 mA. Water was freely available and Purina lab chow was measured to the nearest gram daily until all the rats, control and experimental, had resumed eating behavior. The criterion for resumption of eating behavior was the consumption within a 24 hour period of 3 or more grams of Purina rat chow. At this time animals also resumed drinking behavior 4 ml or more. Eventually, all animals consumed 15 or more grams of food daily. Then they were anesthetized and perfused with isotonic saline and 10% formalin. The brains were extracted, frozen, and sliced at 60μ through the lateral hypothalamic-medial forebrain bundle region until electrode tracts became apparent. This tissue was then mounted and stained with cresylecht violet so that verification of the electrode placement could be made.

Results

Following implantation of the electrodes, all the animals showed aphagia and adipsia, similar to the type produced after electrolytic lesions of the lateral hypothalamic area. The length of time to recovery of eating

behavior, however, depended upon whether or not the animal received electrical stimulation of the lateral hypothalamic-medial forebrain bundle area. The stimulated and non-stimulated groups recovered in 2.4 and 5.8 days, respectively ($p < 0.02$, 2-tailed t-test, $df = 8$). In no case did we observe stimulation bound feeding.

The histology revealed that all electrodes were within the lateral hypothalamic-medial forebrain bundle region. Destruction of tissue from the electrode was basically the same in both the control and experimental groups (Figure 3).

In a series of pilot animals ($n=7$) used to determine the proper coordinates for this study, it was found that electrodes that were dorsal or medial to the most lateral aspects of the lateral hypothalamus, which left intact the hypothalamus striatal fibers, did not produce aphagia or adipsia.

Discussion

The results of this study seem to indicate that electrical stimulation through the same electrodes that induce aphagia by means of a mechanical lesion shortens the post-lesion recovery period. Previous studies have demonstrated that this recovery period may be modified by altering brain norepinephrine. Systemic injections, three days prior to lateral hypothalamic lesions, of

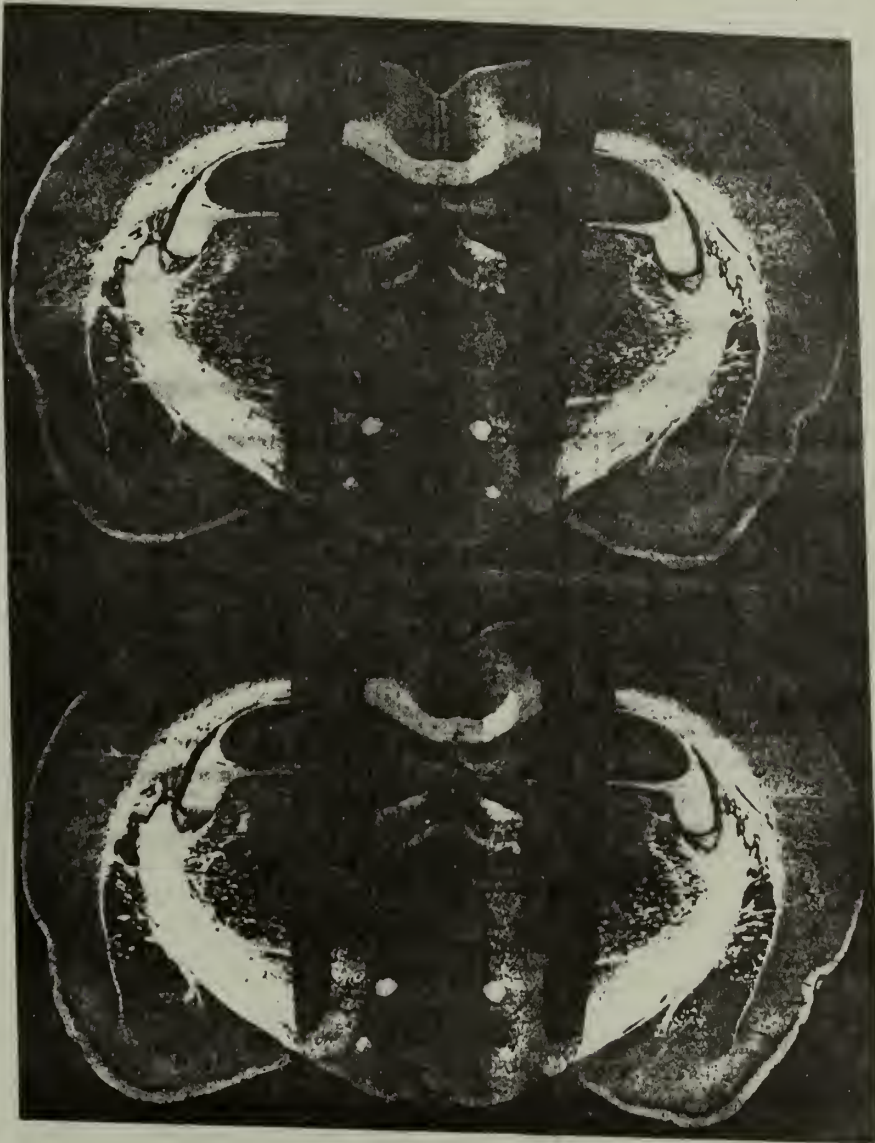


Figure 3. Histology of a typical control (upper) and experimental (lower) animals showing the casts left by the electrodes.

α -methyl-p-tyrosine, which reduces brain norepinephrine, shortens the length of the recovery period, probably as a result of a denervation supersensitivity (Glick, Greenstein and Zimmerberg, 1972). Similarly, administration of the pancreatic hormones, insulin and glucagon, five days prior to surgery shortens or lengthens, respectively, the recovery period (Experiment 1), perhaps by altering norepinephrine synthesis.

These studies along with the evidence that electrical stimulation of the lateral hypothalamic-medial forebrain bundle region changes norepinephrine levels in the hypothalamus (Stein and Wise, 1969) and that deposition of norepinephrine in the brain following lateral hypothalamic lesions shortens the recovery phase (Berger, Wise, and Stein, 1971), leads to the tentative conclusion that in the present investigation the levels of norepinephrine in the lateral hypothalamic-medial forebrain bundle region may have been altered by the electrical stimulation. This in turn could have been responsible for hastening of the recovery after lateral hypothalamic lesions in the stimulated group. However, the possibility exists that this shortened recovery period came about from the concomitant stimulation of dopaminergic fibers of the nigrostriatal system coursing through the hypothalamus at this level.

EXPERIMENT 3

The Generalization of a Phenomenon:

The Effect of Para-chlorophenylalanine on Septal Rage

Until recently little work has been done on the modification of the recovery period which follows neurological damage. It has been demonstrated that this period is modifiable, at least in the feeding system, by certain pre-surgical manipulations. However, little work on generalizing this phenomenon to other neurological systems has been performed. Since ragic behavior which follows septal lesioning is known to disappear (recovery of normal emotionality) with the handling of the animal (Brady and Nauta, 1954), I chose to study whether this behavior could be modified by pre-surgical treatment. Since insulin has been found to alter the recovery of feeding (Experiment 1) and since para-chlorophenylalanine (PCPA) has been found to reduce septal rage when administered after surgery (Dominguez and Longo, 1970), these two compounds have been chosen for the pre-surgical treatment.

Method

Subjects:

Forty-eight male albino rats were housed individually in a temperature controlled room ($72^{\circ} \pm 2^{\circ}$). Illumination

was provided by standard fluorescent ceiling lights (On at 0600, off at 1800). Food and water were available ad libitum throughout the experiment.

Procedure:

Following a week adaptation the rats were randomly assigned to one of three groups: an insulin pre-treatment group, a 2-day pre-treatment PCPA group and a 5-day pre-treatment PCPA group. For five days prior to surgery half of the animals in the insulin group were given 3 units of insulin in a volume of 0.2 ml subcutaneously at 0800 and 2000 hours (INS₅), the other half served as injection controls (C-INS₅). Eight rats were given 200 mg/kg of PCPA in a volume of 0.2 ml at 0800 hours for two days prior to surgery (PCPA₂), the other eight rats were injection controls (C-PCPA₂). For five days prior to surgery eight rats were given 200 mg/kg of PCPA in a volume of 0.2 ml (PCPA₅), the remaining eight rats served as injection controls (C-PCPA₅). All injections were performed under completely blind conditions and were discontinued 24 hours before surgery.

Following the injection series all animals received bilateral lesions of the septal area. These lesions were made under Nembutal anesthesia (40 mg/kg) with the aid of a stereotaxic instrument, by passing anodal current of 3 mA for 30 seconds through an insulex coated 0.5 mm in

diameter stainless steel electrode exposed 0.5 mm at the tip. The stereotaxic coordinates with the incisor bar at zero were: 10.6 mm anterior to the interaural line, 0.8 mm lateral to the midsagittal sinus, and 5.2 mm below the surface of the dorsal cortex.

After surgery the rats were returned to their home cages. On the day following surgery behavioral testing was commenced. This testing consisted of five measures, which have been used in the past to rate septal rage (Brady and Nauta, 1954). Four of these measures consisted of subjective measures of the ragic behavior produced by a poke to the animal's flank, a poke to the animal's nose, the animal's resistance to capture, and the animal's vocalization during handling. All ratings were on a scale of 0 to 6. A fifth measure consisted of the animal's habituation to a poke to the flank. Animals were considered to have habituated when there was no response to three successive pokes. Behavioral testing was done for the first eight days following surgery. Following this time the animals were sacrificed, and histological verification of the lesion placements was done.

Results

At the conclusion of the experiment only 38 out of the original 48 animals were included in the statistical

computations due to either death at the time of surgery or to the incorrect placement of the lesions. Thus the INS_5 and $C-INS_5$ group was comprised of 12 rats (6 in each group), the $PCPA_2$ and $C-PCPA_2$ group of 12 rats, and the $PCPA_5$ and $C-PCPA_5$ group contained 14 rats. Following surgery all rats demonstrated, to some extent, the typical hyperirritability ("rage") which accompanies septal ablation. However, the intensity of the irritability depended upon the pre-treatment the animal had received.

A comparison of all the saline controls revealed a high degree of rage following septal lesions (between 4 and 6 on the subjective rating scales). Furthermore, they responded repeatedly to the poke to the flank.

Comparison between the $C-INS_5$ and INS_5 animals and between the $C-PCPA_2$ and $PCPA_2$ animals revealed no differences in the four subjective rating scales. The $PCPA_2$ rats showed a faster habituation to the flank poke than their controls (Analysis of Variance, $F(1, 10) = 12.7$, $p < 0.001$). This was not the case for the INS_5 groups (see Figure 4, top and middle rows).

The animals pre-treated with PCPA five days prior to surgery ($PCPA_5$), showed low scores on all the behavioral irritability tests except the poke to the flank (poke to nose, $F(1, 12) = 3.5$, $p < 0.05$; resistance to capture, $F(1, 12) = 3.9$, $p < .05$; vocalization, $F(1, 12) =$

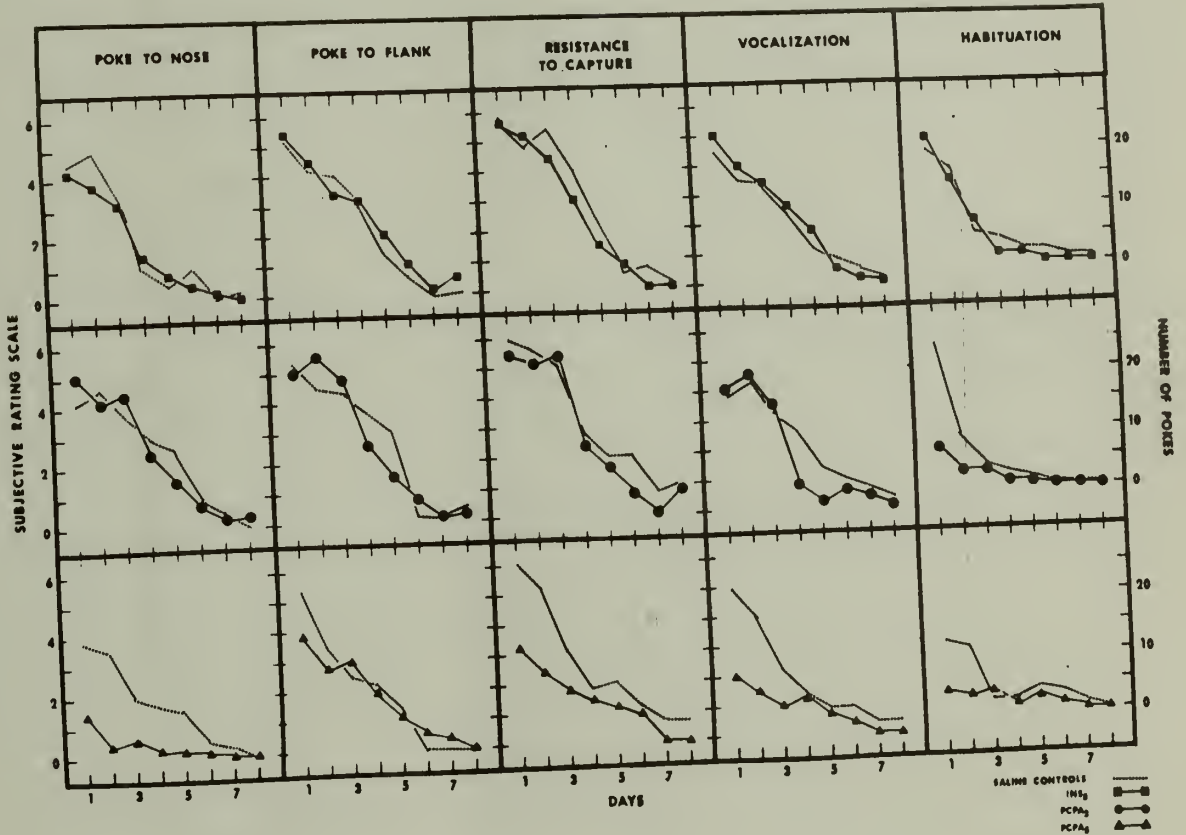


Figure 4. Subjective ratings of rage and habituation to poke following septal lesions. First row: The effect of 5 days Insulin pre-treatment. Second row: The effect of 2 days PCPA pre-treatment. Third row: The effect of 5 days PCPA pre-treatment.

7.4, $p < 0.01$. Furthermore, they also demonstrated a faster habituation to the flank poke than their controls $F(1, 12) = 3.9$, $p < 0.05$). (See Figure 4, bottom row.)

All six groups showed a recovery of emotional behavior over the eight days following surgery on all the behavioral tests ($p < 0.001$). Interaction effects between days and pre-treatments was found only for the PCPA₅ animals and their controls (poke to nose, $F(7, 84) = 2.4$, $p < 0.025$; resistance to capture, $F(7, 84) = 2.03$, $p < 0.05$; habituation to poke, $F(7, 84) = 4.6$, $p < 0.001$).

No differences were found across groups in terms of lesion placements or to the extent of the tissue damaged. Lesions encompassed the whole septal area including the lateral and medial septum, the dorsal aspect of the diagonal bands of Broca and parts of the septal fornix (see Figure 5).

Discussion

The present findings indicate that it is possible to greatly attenuate the hyperirritability that follows lesions of the septum by the appropriate pre-surgical treatment. Thus pre-treatment with PCPA, five days prior to surgery reversed the consequences of septal lesions, while pre-treatment with PCPA two days prior to surgery, or with insulin had no effect.

It is known that a single injection of PCPA results

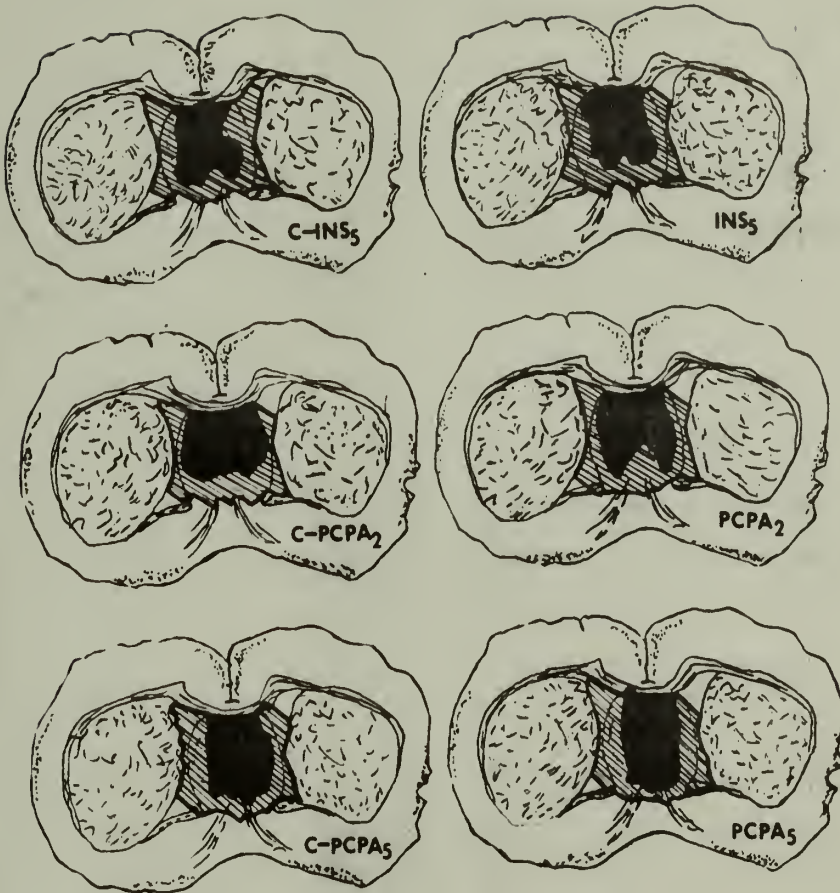


Figure 5. Diagrammatic representation of the lesion placements. Black area = minimum extent of lesion. Striped area = maximum extent of lesion.

in a progressive decrease in whole brain serotonin of rats (Koe and Weissman, 1966). Such treatment does not interfere with catecholamine metabolism. PCPA causes a reduction in brain serotonin by inhibiting the enzyme tryptophan hydroxylase (Jequier, Lovenberg, and Sjoerdsma, 1969), which converts tryptophan to 5-hydroxytryptophan (the rate limiting step in the formation of serotonin).

Serotonergic fibers are known to ascend from the raphe nuclei in the brain stem and to distribute throughout the telencephalon, including the septum (Anden, Dahlstrom, Fuxe, Larsson, Olson, and Ungerstedt, 1966). Destruction of the raphe nuclei leads to a reduction of serotonin within the septum, even though it has no effect on the activity of tryptophan hydroxylase. Furthermore, injections of PCPA lead to virtual depletion of tryptophan hydroxylase in all areas of the telencephalon, except the septum (Harvey and Gal, 1974). This suggests that the tryptophan hydroxylase that is found within the septum is not part of the serotonergic terminals derived from midbrain.

Previously, it was reported that injections of PCPA produce an attenuation of the rage syndrome in rats with septal lesions (Dominguez and Longo, 1969). However, it is hard to establish any relationship between the inhibition of the hyper-reactivity by PCPA and the brain content

of serotonin since maximum sedative effects were observed within 2 hours, a time course quite different from that followed by the serotonin depletion. The reduction in ragic behavior produced by Dominguez and Longo (1969) following septal lesions, was not due to the direct action of PCPA on septal serotonin.

It can be hypothesized that the pre-treatment with PCPA, in the present study, may have caused an alteration in another system functionally related to the septum, resulting in the reduction of the hyperirritability that followed the septal lesions. The above contention is partially supported by the fact that septal lesions produce a 12-14% reduction in serotonin over a period of thirty-five days (Heller, Harvey, and Moore, 1962). This could, in turn affect other neural systems. Along with this progressive depletion of serotonin remains the fact that although five days pre-treatment with PCPA was effective in reducing rage following septal lesions, two day pre-treatment had no effect. That such an effect may be primarily serotonergic is supported by the findings that pre-treatment with insulin had no effect on the septal hyperirritability. Insulin has been postulated to influence the adrenergic system in the central nervous system (Viveros, Arqueros, Connett, and Kirschner, 1969; Weiner and Mosimann, 1970).

To summarize, the results of this study indicate that it is possible to modify septal rage by surgical pre-treatment. However, the effect is specific to pre-treatment for 5 days with PCPA suggesting that the brain mechanism mediating this effect is serotonergic in origin and requires a minimum amount of time for the PCPA to act.

EXPERIMENT 4

The Effects of Dark and Light on the
Recovery Period Following Diencephalic Lesions

Research during the last four decades has demonstrated that illumination cycles may influence or are correlated with many physiological and behavioral functions: for example, liver glycogen (Sollberger, 1964), body temperature (Kleitman, Teitelbaum, and Hoffman, 1937), certain adrenal hormones (Migeon, Tyler, Mahoney, Florentine, Castle, Bliss and Samuels, 1956; Halberg, Visscher, and Bittner, 1953), brain levels of neurotransmitters such as acetylcholine (Hanlin, Massarelli, and Costa, 1970), norepinephrine and serotonin (Schevin, Harrison, Gordon, and Pauly, 1968).

Recently, it has been demonstrated that the effects of certain brain lesions may vary depending on the conditions to which the organisms are exposed in the immediate pre-surgical period (Powley and Keesey, 1970; Harrell and Balagura, 1974; Balagura and Harrell, 1974; Glick, Greenstein and Zimmerberg, 1972). Experimental evidence suggests that modification of functional recovery may be secondary to alterations in the levels of brain neurotransmitters before or immediately after lesioning (Glick, Greenstein, and Zimmerberg, 1972; Harrell, Experiment 1; Berger, Wise and Stein, 1971, 1973). In light of the

above mentioned findings, and since environmental illumination can alter brain neurotransmitters, it is likely that the consequences of neurosurgery would vary depending on the illumination preceeding or following surgery.

Method

Subjects:

Thirty male albino rats weighing between 350-400 grams (approximately 90 days old) were adapted for one week to individual cage housing, Purina lab chow, and an illumination cycle of 12 hours of light followed by 12 hours of dark (lights on at 0600, off at 1800). Food intake and body weight were recorded daily throughout the experiment.

Procedure:

Following the adaptation period, and five days before surgery, ten animals were placed in non-cycling constant light, ten animals were placed in non-cycling constant dark, and ten animals were maintained on a 12 hour dark-light cycle. During this time the animals underwent daily behavioral motor testing. As described earlier (Balagura, Wilcox, and Coscina, 1969) these tests consisted of measuring latency of a rat to "step-down" from a 3.5 in. wide, 5 in. long platform, 3 in. above the floor, to remove a forepaw from the experimenter's index finger,

approximately 1 in. above the table surface ("waxy flexibility"), and to regain a horizontal position after being placed in a vertical position on the front part of its home cage such that the hind quarters were hanging over the top edge of the cage and the front paws were grasping the inside of the cage front, approximately 1/2 to 3/4 of the way down the cage front ("horizontal stabilization"). Maximum time allotted for each task on any given trial was 60 seconds.

Following the five days of pre-surgical behavioral motor testing under a given illumination condition, all animals received bilateral lateral hypothalamic lesions. Direct anodal current of 1.5 mA was delivered for 25 seconds through an Insulex-coated stainless steel electrode (0.5 mm in diameter) exposed 0.5 mm at the tip. The stereotaxic coordinates with the skull horizontal between bregma and lambdoid were: 7.0 mm anterior to the interaural line, 2.0 mm lateral to the midsagittal sinus, and 7.7 mm below the dorsal surface of the cortex. All animals received lateral hypothalamic lesions between 0800 and 1200 (EST), except for five of the 10 animals that remained under cycling conditions, which received their lesions between 2000 and 0000 (EST). Following surgery, five of the animals which had been in the dark were returned to their pre-surgical illumination

environment (D-D), the five remaining animals were shifted to the constant light condition (D-L). Five of the constant light animals were returned to that condition (L-L), while five were shifted to constant dark (L-D). The animals remaining on a 12 hour light-dark cycle were returned to their original environment. However, five of these animals received lateral hypothalamic lesions during the light part of the cycle (C_1), while five underwent surgery during the dark part of the cycle (C_d). Motor testing resumed on the day following surgery and continued for eight days. At the end of this time the animals were sacrificed and their brain removed, sliced at $60\mu\text{m}$, and stained with cresylecht-violet for histological verification of the lesion placement.

Results

In all cases, surgery was followed by typical aphagia and adipsia that persisted for the duration of the experiment (Teitelbaum and Stellar, 1954). As shown in Figure 1 (2nd row), diencephalic lesions in the C_1 and C_d rats caused severe impairment on all three tasks (step-down, $p < 0.001$; horizontal stabilization, $p < 0.001$; waxy flexibility, $p < 0.001$; two-tailed matched t-test ($df = 8$) between preoperative and post operative performance), irrespective of the time in which the lesions were performed. No differences were found between these two

groups with respect to degree of impairment or time to recover their preoperative ability to perform all the tasks.

Intact animals kept in constant darkness showed longer latencies on step-down, $F(1,8) = 8.4, p < 0.025$; Analysis of Variance, D-D vs. L-L, and D-L vs. L-D) and waxy flexibility tasks $F(1,8) = 7.2, p < 0.05$; D-D vs. L-L, and D-L vs. L-D) than animals kept in constant light. Diencephalic lesions in the L-L groups resulted in the typical task impairment (Figure 6, 3rd row; $p < 0.001$ all tasks, two-tailed t-test (df = 8) matched). However, the D-D lesioned animals showed no impairment on horizontal stabilization ($p > 0.05$ t-test, df = 8) and waxy flexibility ($p < 0.05$ t-test, df = 8) tasks, and a slight impairment on the step-down task ($p < 0.05$ t-test, df = 8). A comparison between D-D and L-L groups following surgery revealed a milder impairment of function in the D-D rats (step-down, $F(1,8) = 7.7, p < 0.025$; horizontal stabilization, $F(1,8) = 23.9, p < 0.001$; waxy flexibility, $f(1,8) = 54.7, p < 0.001$; Analysis of Variance).

As can be seen in Figure 6 (4th row) following lateral hypothalamic lesions the L-D rats had longer latencies than the D-L rats on all tasks (step-down, $F(1,8) = 5.34, p < 0.05$; horizontal stabilization, $F(1,8) = 21.0, p < 0.005$; waxy flexibility, $F(1,8) = 6.0, p < 0.05$;

Analysis of Variance). All L-D animals showed some degree of impairment on all three tasks following surgery ($p < 0.001$ on step-down and horizontal stabilization; $p < 0.01$ on waxy flexibility; two-tailed matched t-test; $df = 8$). All D-L rats showed impairment on the step-down ($p < 0.01$ t-test, $df = 8$) and waxy flexibility ($p < 0.05$ t-test, $df = 8$) tasks. They showed no impairment of the horizontal stabilization task. Moreover, a comparison of task scores of L-L versus L-D on the first day following surgery revealed that the L-D rats were less impaired on all three tasks ($p < 0.01$, all tasks, two-tailed t-test, $df = 8$).

Animals from all groups improved their task scores over time. Interaction effects between groups and time were found only in the D-D versus L-L groups for the horizontal stabilization $F(7,56) = 3.2$, $p < 0.001$, and waxy flexibility tasks $F(7,56) = 3.1$, $p < 0.005$.

Histological analysis of the lesioned sections revealed that in all cases, the diencephalon had sustained bilateral lesions approximately 1 mm^3 , that involved the inner aspects of the internal capsule, the lateral third to $1/2$ of the lateral hypothalamic-medial forebrain bundle area, leaving at least 0.5 mm of undamaged tissue lateral to a vertical line passing through the outer edge of the fornix and mammillothalamic tracts. The dorsal

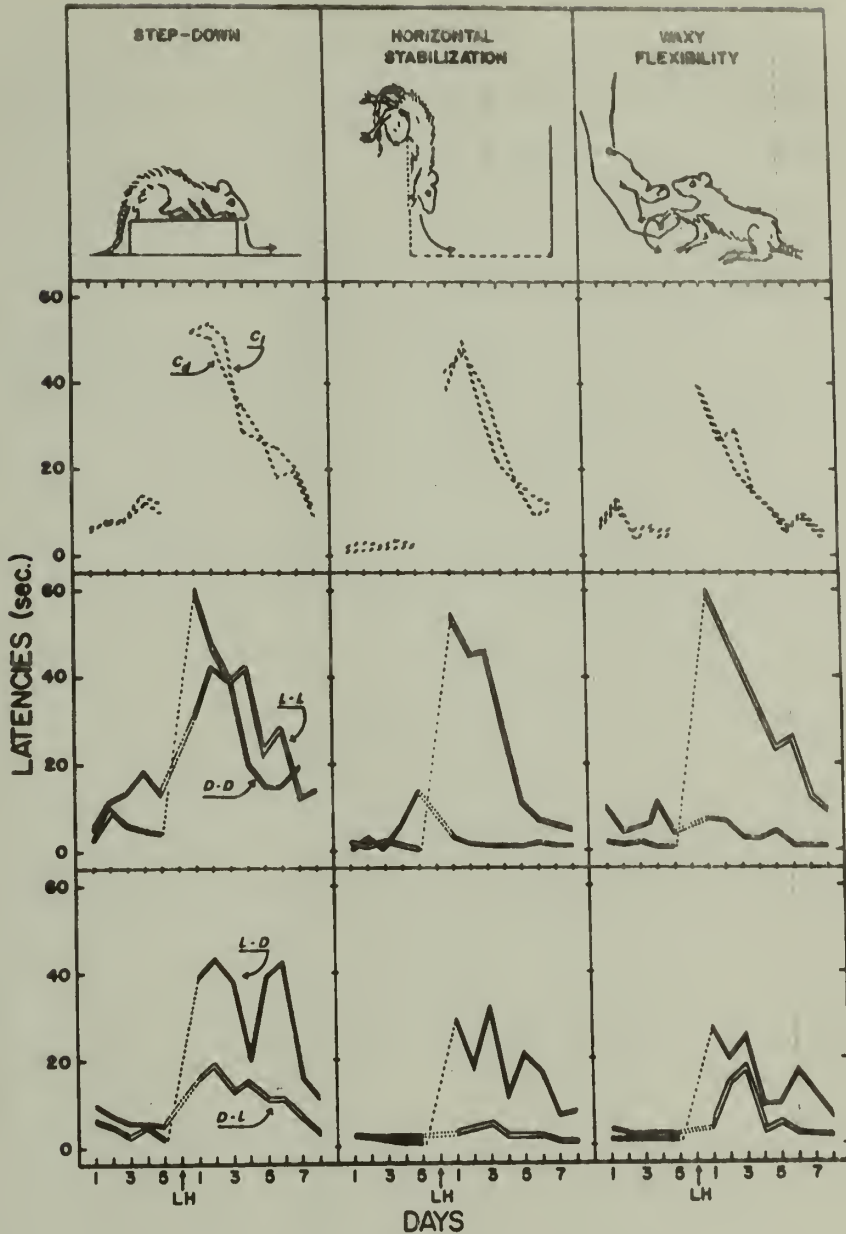


Figure 6. Latencies to execute motor tasks before and after surgery. First row: Illustration of motor tasks (arrows indicate type of response expected). Second row: Effects of lateral hypothalamic lesions in rats kept on a 12 hour light-dark cycle (C_2 = lesioned during dark, C_1 = lesioned during light). Third row: Effects of lateral hypothalamic lesions in animals maintained in constant dark (D-D) and light (L-L) before and after surgery. Fourth row: Effects of lateral hypothalamic lesions in rats kept in constant dark before, but shifted to constant light after surgery (D-L), and vice versa (L-D).

extension involved the most ventral part of the fields of Forel. Lesions did not vary across experimental groups (Figure 7).

Discussion

These results clearly demonstrate a dissociation between the motor and feeding aberrations caused by lateral hypothalamic lesions, corroborating previous findings (Balagura, Wilcox, and Coscina, 1969). Motor deficits, as measured by the motor tasks, gradually returned towards normality over an eight day period in all animals. The motor recovery in the C_1 and C_d groups was not differentially affected by the time of surgery. However, maintaining the animals under a constant light condition profoundly affected the degree of motor impairment that followed lesioning. A constant dark environment prior to surgery diminished the severity of the post-surgical motor defects regardless of the illumination condition following lesions (D-D and D-L on step-down task; D-L on waxy flexibility), and totally prevented certain motor impairments (D-D and D-L on horizontal stabilization; D-D on waxy flexibility). Furthermore, post-surgical constant darkness exerted an ameliorative effect on motor performance in animals previously kept in constant light.

Alteration of neurotransmitters during the

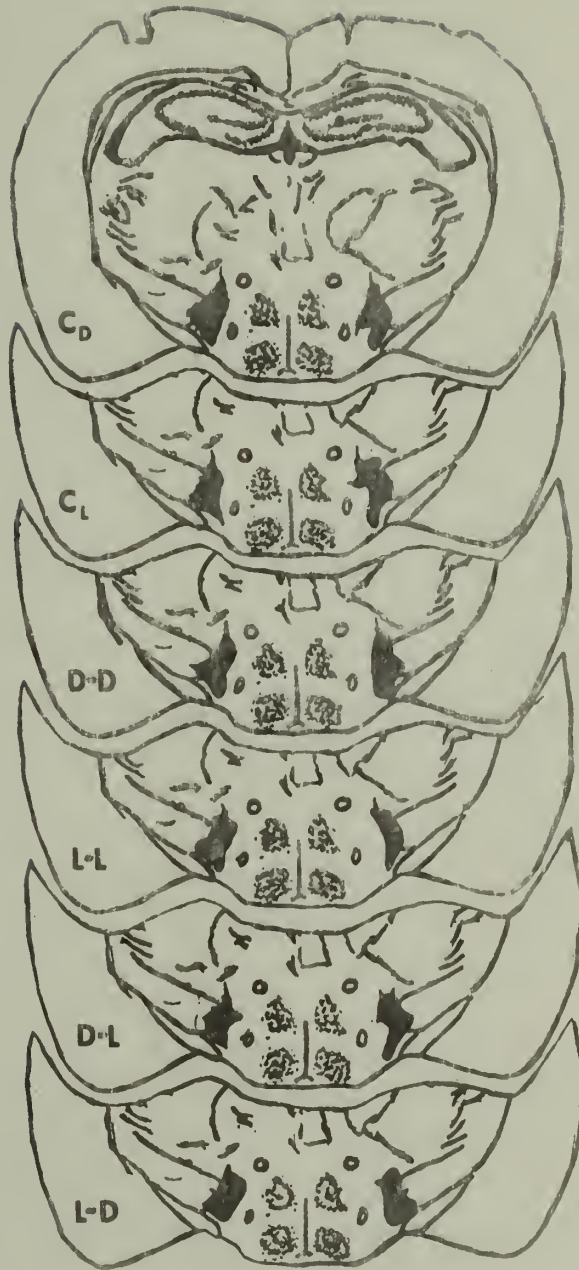


Figure 7. Histology from representative animals in each group. Lesions in all animals encompassed the lateral hypothalamus, the medial edge of the internal capsule and the ventral aspects of the fields of Forel.

peri-surgical period have been shown to modify the consequences of brain damage (Glick, Greenstein, and Zimmerberg, 1972; Harrell, Experiment 1; Berger, Wise and Stein, 1971, 1973). It is not clear whether neurotransmitter levels vary as a result of an intrinsic rhythm, or to an entrainment to the environmental lighting. However, it is known that brain levels of both serotonin and acetylcholine are depressed during the dark portion of a 12 hour dark-light cycle, while norepinephrine levels are increased. Dopamine does not have a clearly defined differential level between dark and light conditions (Schevin, Harrison, Gordon, and Pauly, 1968). If neurotransmitters levels are influenced by a given illumination condition, it could be hypothesized, in the present experiment, that the sparing effects of constant darkness are in some way related to the differential levels of acetylcholine, serotonin, dopamine, and norepinephrine existent at the time of surgery and immediately thereafter. Supporting evidence comes from Ungerstedt's report (1971) of increased motor deficiencies following destruction of central dopaminergic fibers. Of course, any alteration of neurotransmitters could bring about modification of cellular organelles, which could in turn influence recovery, for example, by denervation supersensitivity. Further research is necessary to understand

the details of how these manipulations may modify recovery.

Irrespective of the specific biochemical and neuro-anatomical changes that result from a given environmental condition, the results provide strong evidence that the consequences of neurosurgery (in animals and perhaps man) may vary greatly contingent upon the pre-surgical preparation of the organism.

GENERAL DISCUSSION

The results presented in the aforementioned experiments have one common element. * They clearly demonstrate that it is possible to induce the reappearance of almost normal behavioral functioning following brain damage.

† The mechanism by which this is accomplished is unknown, however, both pre- and post-surgical manipulations are capable of altering the recovery period.

* It can be hypothesized that pre-surgical treatments influence the central nervous system in one of two manners, or a combination of both. First, on a macroscopic level, surgical pre-treatment may alter whole brain structures (i.e., lateral hypothalamus, septum, hippocampus) in such a way as to modify their ability to take over the functions of another area destroyed by surgical ablations. Second, on a more microscopic level, surgical pre-treatment may affect subcellular organelles or cellular metabolism to affect a change in the levels of neurotransmitters, post-synaptic receptors, various organelles associated with collateral sprouting, etc.

No matter how the pre-surgical treatments are translated into physiological and/or biochemical alterations within the central nervous system, once these changes have occurred surgical ablations are being performed on an altered organism. † Under these circumstances, surgical

destruction in the central nervous system will lead to a different set of events than when performed under no treatment conditions. These events may be hypothesized to occur at both a physiological and behavioral level.

* Thus animals, which have undergone pre-treatment with PCPA, insulin, glucagon, or darkness demonstrate an altered recovery pattern when compared to their controls.

* It is interesting to note that not all pre-surgical treatments are capable of altering the same neurological/behavioral system. Thus, insulin which is quite effective at reducing aphagia consequent to lateral hypothalamic lesions, has no effect on ragic behavior following septal lesions. Likewise, darkness which reduces motor dysfunction following lateral hypothalamic lesions, does not ameliorate the co-existing aphagia. * These facts suggest that each brain system can be modified only by a specific pre-surgical treatment.

Post-surgical manipulations may also lead to a modification of the central nervous system. In this case, however, the alterations are produced during the days following surgical ablations. * Like pre-surgical manipulations, post-surgical treatments may influence the subject at both a macroscopic or microscopic level to alter the recovery process.

The findings presented in the four experiments of

this dissertation provide the initial demonstration of perhaps a very universal phenomenon. At present, one can re-interpret the results with multiple-stage lesions and those of infancy versus adulthood lesions in the light of surgical pre-treatments. In the former case, the unilateral lesion may better "prepare" the organism for the consequences of the second lesion, while in the latter case age may affect the speed and completeness of the recovery process following surgical ablations.

Regardless of how the multiple-stage lesions and infancy lesion literature is interpreted, the implications provided by the experiments involving pre-surgical manipulations are far-reaching. In the basic sciences experimenters will, in the future, have to consider many variables, which may not have been thought to be important when performing neurosurgery; i.e., influence of the temperature on effectiveness of lesions associated with learning deficits, the phase of the estrus cycle when lesions are performed, etc. On a more clinical level, neurosurgeons, in the future, may have to "prepare" their patients for brain surgery so that the results are not as deleterious or variable.

REFERENCES

- Arnand, B.K. and Brobeck, J.R. Localization of a feeding center in the hypothalamus of the rat. Proceedings of Society of Experimental Biology and Medicine. 1951, 77: 323-324.
- Anden, N.E., Dahlstrom, A., Fuxe, K., Larsson, K. Olson, L. and Ungerstedt, U.Y. Ascending monoamine neurons to the telencephalon and diencephalon. Acta Physiologica Scandinavica, 1966, 67: 313-326.
- Balagura, S. and Harrell, L.E. The lateral hypothalamic syndrome: Its modification by obesity and leanness. Physiology and Behavior, 1974 (in press).
- Balagura, S., Wilcox, R.H. and Coscina, D.V. The effect of diencephalic lesions on food intake and motor activity. Physiology and Behavior, 1969, 4: 629-633.
- Beach, F.A. The neural basis of innate behavior: Relative effect of partial decortication in adulthood and infancy upon the maternal behavior of the primiparous rats. Journal of Genetic Psychology, 1938, 53: 109-148.
- Benjamin, R.M. and Thompson, R.F. Differential effects of cortical lesions in infant and adult cats on roughness discrimination. Experimental Neurology, 1969, 1: 305-321.

- Berger, B.D., Wise, C.D. and Stein, L. Norepinephrine: Reversal of anorexia in rats with lateral hypothalamic damage. Science, 1971, 172: 281-284.
- Berger, B.D., Wise, C.D. and Stein, L. Nerve growth factor: Enhanced recovery of feeding after lateral hypothalamic damaged. Science, 1973, 180: 506-509.
- Brady, J.V. and Nauta, W.J.H. Subcortical mechanisms in emotional behavior: Affective changes following septal forebrain lesions in the albino rat. Journal of Comparative and Physiological Psychology, 1953, 46: 339-346.
- Cheng, M.F., Rozin, P. and Teitelbaum, P. Starvation retards development of food and water regulation. Journal of Comparative and Physiological Psychology, 1971, 76: 206-218.
- Chow, K.L. and Randall, N. Learning and retention in cats with lesions in reticular formation. Psychonomic Science, 1964, 1: 259-260.
- Denny-Brown, D. The nature of apraxia. Journal of Nervous and Mental Disease, 1958, 126: 9-32.
- Denny-Brown, D. and Chambers, R.A. The parietal lobe and behavior. Research Publication, Association for Research in Nervous and Mental Disease, 1958, 36: 35-117.

- Dominguez, M. and Longo, V.G. Taming effects of para-chlorophenylalanine on septal rats. Physiology and Behavior, 1969, 4: 1031-1033.
- Dominguez, M. and Longo, V.G. Effect of p-chlorophenylalanine, α -methyl-p-tyrosine and other indol- and catechol- amine depletors on the hyperirritability syndrome of septal rats. Physiology and Behavior, 1970, 5: 607-610.
- Doty, R.W. Functional significance of the topographical aspect of the retino-cortical projection. In: The Visual System: Neurophysiology and Psychophysics. R. Jung and H. Kornhuber, (Eds.), Springer, Berlin, 1961: 228-247.
- Epstein, A.N. and Teitelbaum, P. Severe and persistent deficits in thirst produced by lateral hypothalamic damage. In: Thirst in the Regulation of Body Water, M. Wayner, (Ed.), London: Pergamon Press, 1964: 395-406.
- Epstein, A.N. and Teitelbaum, P. Specific loss of the hypoglycemic control of feeding in recovered lateral rats, American Journal of Physiology, 1967, 213: 1159-1167.
- Glick, S.D., Greenstein, S. and Zimmerberg, B. Facilitation of recovery by α -methyl-p-tyrosine. Science, 1972, 177: 534-535.

- Grossman, S.P. Eating and drinking elicited by direct adrenergic stimulation of hypothalamus. Science, 1960, 132: 301-310.
- Halberg, F., Visscher, M.B. and Bittner, J.T. Eosinophil rhythm in mice: range of occurrence effects of illumination, feeding and adrenalectomy. American Journal of Physiology, 1953, 17: 109-122.
- Hanin, L., Massarelli, R. and Costa, E. Acetylcholine concentration in rat brain: diurnal oscillation. Science, 1970, 170: 341-342.
- Harrell, L.E. and Balagura, S. The influence of ovarian hormones on the recovery period following lateral hypothalamic lesions. Journal of Comparative and Physiological Psychology, 1974, (in press).
- Harvey, J.A. and Gal, E.M. Septal tryptophan-5-hydrolase: Divergent response to raphe lesions and para-chloro-phenylalanine. Science, 1974, 183: 869-871.
- Heller, A., Harvey, J.A. and Moore, R.Y. A demonstration of a fall in brain serotonin following central nervous system lesions in the rat. Biochemical Pharmacology, 1962, 11: 859-866.
- Hines, M. The development and regression of reflexes, postures, and progression in the young Macque. Carnegie Institute of Washington, 1942, 54: 153-209.

- Jequier, E., Lovenberg, W. and Sjoerdsma, A. Tryptophan hydroxylase inhibition: The mechanism by which p-chlorophenylalanine depletes rat brain serotonin. Molecular Pharmacology, 1967, 3: 274-278.
- Kennard, M.A. Age and other factors in motor recovery from precentral lesions in monkeys. American Journal of Physiology, 1936, 115: 138-146.
- Kennard, M.A. Reorganization of motor function in cerebral cortex of monkeys deprived of motor and premotor areas in infancy. Journal of Neurophysiology, 1938, 1: 477-496.
- Kennard, M.A. Cortical reorganization of motor function: Studies on a series of monkeys of various ages from infancy to maturity. Archives of Neurology and Psychiatry, 1942, 8: 227-240.
- Kleitman, N., Teitelbaum, S., and Hoffman, H. The establishment of the diurnal temperature cycle. American Journal of Physiology, 1937, 119: 48-52.
- Kling, A. Amygdalectomy in the kitten. Science, 1962, 137: 429-430.
- Lashley, K.S. Brain Mechanisms and Intelligence. Dover, New York: 1963.
- Migeon, C.J., Tyler, F.H., Mahoney, J.P., Florentin, R.A.M., Castle, H., Bliss, E.L. and Samuels, L.T. A diurnal variation in plasma levels and urinary excretion of

- 17-hydroxycorticosteroids in normal subjects, night workers, and blind subjects. Journal of Clinical Endocrinology and Metabolism, 1956, 16: 622-633.
- MacKay, E.M., Callaway, J.W. and Barnes, R.H. Hyperalimentation in normal animals produced by protamine insulin. Journal of Nutrition, 1940, 20: 59-66.
- Powley, T.L. and Keesey, R.E. Relationship of body weight to the lateral hypothalamic feeding syndrome. Journal of Comparative and Physiological Psychology, 1970, 70: 25-36.
- Raisler, R.L. and Harlow, H.F. Learned behavior following lesions of posterior association cortex in infant, immature, and preadolescent monkey. Journal of Comparative and Physiological Psychology, 1965, 60: 167-174.
- Raisman, G. Neuronal plasticity in the septal nuclei of the adult rat. Brain Research, 1969, 14: 25-48.
- Rosen, J., Stein, D. and Butters, N. Recovery of function after serial ablation of prefrontal cortex in the Rhesus monkey. Science, 1971, 173: 353-356.
- Salter, J.M. Metabolic effects of glucagon in the wistar rat. The American Journal of Clinical Nutrition, 1960, 8: 535-539.

- Scheving, L.E., Harrison, W.H., Gordon, P. and Pauly, J.E.
Daily fluctuation (circadian and ultradian) in biogenic amines of the rat brain. American Journal of Physiology, 1968, 214: 166-173.
- Sollberger, A. The control of circadian glycogen rhythms. Annual New York Academy of Sciences, 1964, 114: 519-554.
- Stein, D.G., Rosen, J.J., Gradiader, J., Mishkin, D. and Brink, J.J. Central nervous system: Recovery of function. Science, 1969, 166: 528-531.
- Stein, L. and Wise, C.S. Release of norepinephrine from hypothalamus and amygdala by rewarding medial fore-brain stimulation and amphetamine. Journal of Comparative and Physiological Psychology, 1969, 67: 189-198.
- Steward, J.W., and Ades, H.W. Learned discrimination performance by monkeys after prolonged postoperative recovery from large cortical lesions. Journal of Comparative and Physiological Psychology, 1952, 45: 119-126.
- Teitelbaum, P. Disturbances in feeding and drinking behavior after hypothalamic lesions. In: Nebraska Symposium on Motivation. M.R. Jones (Ed.), Lincoln: University of Nebraska Press, 1967, 39-69.

- Teitelbaum, P. The biology of drive. In: Neurosciences: A Study Program. G.G. Quarten, T.T. Melnechuk and F.O. Schmitt, (Eds.), New York: Rockefeller University Press, 1967.
- Teitelbaum, P. and Epstein, A.N. The lateral hypothalamic syndrome: Recovery of Feeding and drinking after lateral hypothalamic lesions. Psychological Review, 1963, 69: 74-90.
- Teitelbaum, P. and Stellar, E. Recovery from failure to eat produced by hypothalamic lesions. Science, 1954, 120: 894-895.
- Teitelbaum, P., Cheng, M.F. and Rosen, P. Development of feeding parallels its recovery after hypothalamic damage. Journal of Comparative and Physiological Psychology, 1969, 67: 430-441.
- Tsang, Y.C. Maze learning in rats hemidecorticated in infancy. Journal of Comparative and Physiological Psychology, 1937, 24: 221-253.
- Tucker, T. and Kling, A. Differential effects of early vs. late brain damage on visual duration discrimination in cat. Federation Proceedings, Federation of American Society for Experimental Biology, 1966, 25: 207.
- Turner, C.D. and Bagnara, J.T. General Endocrinology. Philadelphia: W.B. Saunders Co., 1971.

- Ungerstedt, U. Adipsia and aphagia after 6-hydroxydopamine induced degeneration of the nigro-striatal dopamine system. Acta Physiologica Scandinavia, 1971, 367: 95-122.
- Viveros, O.H., Arqueros, L., Connett, R.J. and Kirschner, N., Mechanism of secretion from the adrenal medulla IV. The fate of the storage vesicles following insulin and reserpine administration. Molecular Pharmacology, 1969, 5: 69-82.
- Wall, P.D. and Egger, M.D. Formation of new connections in adult rat brain after partial deafferentiation. Nature, 1971, 232: 542-546.
- Weiner, N. and Mosimann, W.F. The effect of insulin on the catecholamine content and tyrosine hydroxylase activity of cat adrenal glands. Biochemical Pharmacology, 1970, 19: 1189-1199.
- Wetzel, A.B., Thompson, V.E., Horel, J.A. and Meyer, P.M. Some consequences of perinatal lesions of the visual cortex in the cat. Psychonomic Science, 1965, 3: 381-382.

