RECOVERY OF SPECIFIC DEFICITS FOLLOWING UNILATERAL LESIONS OF THE LATERAL HYPOTHALAMUS IN RATS

by

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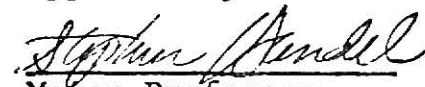

Major Professor

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It has been suggested that a dual hypothalamic mechanism functions to control food intake (Stellar, 1954). Satiety (termination of eating) is controlled by activity in the ventromedial nucleus of the hypothalamus (VMH) (Heatherington and Ranson, 1940). The initiation of feeding and drinking behavior is controlled by the lateral hypothalamic area. Bilateral lesions of the lateral hypothalamus (LH) produce a complete cessation of feeding and subsequent death from starvation (Anand and Brobeck, 1951). Teitelbaum and Stellar (1954) extended these findings to demonstrate that adipsia (refusal to drink) accompanied aphagia in animals with LH lesions.

Teitelbaum and Stellar (1954) also showed that rats with bilateral LH lesions eventually recover from aphagia and adipsia if they are kept alive by forced feeding via a naso-gastric tube. This recovery from aphagia and adipsia progresses through an orderly sequence of changes in feeding and drinking, the "lateral hypothalamic syndrome" (Teitelbaum and Epstein, 1962): At first, animals with bilateral LH lesions refuse all food and water (Stage I). They ignore food and water near them, and actively repel any that is forced upon them. Since their behavior in this first stage is similar to that seen in normal rats exposed to quinine, this suggests that mouth contact with food and water has become highly aversive to rats with lateral lesions. The

aversion to oral food and water cannot explain the aphagia and adipsia. Rodgers, Epstein and Teitelbaum (1965) prepared animals with naso-gastric tubes to enable them to eat without taste or smell. After LH lesions, these animals refused to feed either by mouth or naso-gastric tube. They, too, rapidly lost weight, and eventually starved to death.

During Stage II, the animals begin to eat small quantities of wet and highly palatable foods (e.g., milk chocolate, chocolate chip cookies, and an eggnog diet) but refuse dry pellets and drink no water. They are anorexic and cannot maintain body weight adequately. Palatable and odorous foods are especially effective in stimulating the animal to investigate and, subsequently, to eat. This feeding is delicately undertaken, however, and does not resemble the vigorous gulping of a starving rat. As Stage II progresses, general activity and interest in food increases. Ultimately the anorexia terminates, and the animal is able to maintain itself by eating highly palatable foods.

In Stage III, animals are able to regulate their caloric intake. They will press a lever to receive food to be eaten or an injection of liquid diet through a chronic naso-gastric tube. Thus, taste and smell are no longer necessary to elicit feeding; ingestion is under the control of caloric regulation. An animal still refuses plain water in Stage III. If given only water,

it refuses to drink, stops eating, and dies of dehydration (Williams and Teitelbaum, 1959). Teitelbaum and Epstein (1962) have shown that the rat in Stage III refuses dry food because it is dehydrated. Animals hydrated intragastrically will eat dry pellets and maintain body weight.

Eventually, most rats enter Stage IV, "recovery". They begin to drink water and maintain their body weight on dry food and water. Superficially, they appear normal. However, more sensitive tests indicate the continued presence of severe deficits in regulation. Rats recovered from LH lesions reject water containing as little as 0.005% weight per volume (w/v) of quinine (Teitelbaum and Epstein, 1962). They will subsequently stop eating, lose weight and die. Normal rats with no other source of fluid will drink quinine solutions up to a concentration of 1%, at which point it becomes toxic. Thus, it appears that rats, ostensibly recovered from lateral lesions, are overly responsive to the palatability of liquids and unable to overcome an aversion to the bitter taste of quinine. Analogous results have been found with feeding. When quinine is mixed with dry Purina powder, the animals stop eating and starve to death.

Teitelbaum and Epstein (1962) injected rats, intraperitoneally, with a hypertonic sodium chloride solution. Normal rats increase their fluid intake and compensate for dehydration.

Recovered lateral animals do not respond, by drinking, after hypertonic saline injections. Instead, they stop eating, lose weight, and, finally, are close to death.

Teitelbaum and Epstein (1962) found that recovered lateral rats are consistent "prandial" drinkers. That is, they drink water in small draughts taken after each morsel of food eaten. This drinking is abolished when small quantities of water are injected into the mouth (Kissileff, 1966). Prandial drinking is probably the result of difficulty in swallowing dry food. Normal animals also engage in food-associated drinking. This drinking is usually in large draughts, averaging about 2 ml., and precedes or follows a large meal of dry food. Prandial drinking is controlled by body need, and disappears if the animal is kept hydrated by water administered intragastrically as well as orally (Kissileff, 1966). If normal rats are deprived of food overnight, they still drink nearly normal amounts of water. Lateral rats fail to do this. They drink little or no water when food is not available also.

Intact rats increase their food intake when hypoglycemia is induced by insulin injections. This additional feeding prevents the coma and convulsions of an uncorrected, and severe, drop in blood sugar level. Epstein and Teitelbaum (1967) injected recovered lateral rats with 1-16 units of crystalline

or 1-8 units of protamine zinc insulin, subcutaneously. Recovered lateral animals are unable to respond normally to a sudden decrease in blood glucose. They do not eat more food in response to the insulin. They either eat nothing or take too little food to counteract the hypoglycemia.

The regulatory deficits found in animals "recovered" from LH lesions seem to constitute relatively permanent deficits. The thirst deficits seen in these rats are of long duration, and, in most cases are permanent (Epstein and Teitelbaum, 1964). A few animals eventually become more responsive to hypertonicity produced by injections of hypertonic saline. Some eventually drink water contaminated with as much as 0.1% quinine. However, the majority of the rats fail to show recovery from thirst deficits before they die. Teitelbaum and Epstein (1962) also report on one rat which failed to respond to hypoglycemia 503 days after LH damage.

The majority of studies on the feeding and satiety centers of the hypothalamus were made using bilateral lesions (or other comparable techniques) to induce changes in feeding and drinking. It has been generally accepted that unilateral lesions produce transient or insignificant effects (e.g., Teitelbaum and Epstein, 1962); however this may not be the case.

Epstein (1960) used cannulae implanted chronically in the hypothalamus. Small quantities of solutions of various chemicals were injected through the cannulae into the ventromedial and lateral areas. Procaine injected bilaterally into the VMH produced significant increases in eating. Feeding was suppressed when procaine was placed bilaterally into the lateral area. Hypertonic saline elicited eating when placed bilaterally in the LH. Conversely, eating was suppressed by bilateral saline injections into the VMH. These results could be repeated reliably using unilateral injections. The results of unilateral lesions of the VMH were investigated by Mayer and Barrnett (1955). After unilateral VMH lesions their animals showed hyperphagia with steady weight gains. The gain in weight was generally less than that seen in comparable rats subjected to bilateral lesions.

Gold (1966) made small unilateral lesions of the lateral hypothalamus in rats which produced up to 4.0 days of aphagia (to dry food) and 5.5 days of adipsia. Once these animals recovered from aphagia, the remaining half of the lateral hypothalamus was lesioned. This two-stage procedure produced the prolonged aphagia and adipsia usually associated with one-stage bilateral lesions. He found that the duration of aphagia and adipsia following a second lesion correlated closely with the duration following initial lesions.

Wampler and Teitelbaum (1967) and Phillips and Mogenson (1968) replicated Gold's findings of aphagia and adipsia with unilateral lesions of the LH. Wampler and Machinton (1968) extended these findings and tested the responses of animals recovered from unilateral lesions to insulin-induced hypoglycemia, saline-induced hyperosmolarity, and water during food deprivation. All tests indicated a significant change from control animals, except saline-induced drinking. In a second experiment, they made lesions slightly more anterior in the hypothalamus. The response to quinine of the recovered rats was measured in addition to the initial three tests. These animals responded normally to saline, and, further, they showed a normal increase in food intake in response to insulin. In both experiments, the responses of the recovered rats lay between those of unoperated controls and those of recovered bilateral animals.

Unilateral lesions of the lateral hypothalamus are useful in the study of the function of this structure. Specifically, one obstacle to the study of recovery from bilateral lesions has been the problem of extremely lengthy periods of time taken for animals to reach Stage IV, recovery of food and water intake. Unilateral lesions have been shown to generate effects comparable to those seen with bilateral lesions, but produce more rapid progression through the stages of recovery. It seems

reasonable to predict that a unilateral lesion will also allow an animal to recover from the underlying physiological deficits found in Stage IV -- if such a recovery is ever possible.

Additionally, Wampler and Machinton (1968) found varying responses to their tests of regulatory deficits of animals recovered from unilateral lesions. It may be that slight variations in lesion placement differentially influence separate regulatory controls in the lateral hypothalamus. Grossman (1960) demonstrated that the feeding and drinking centers of the LH can be separated chemically with stimulation by different chemicals. Eating and drinking deficits may also be produced separately by lesions in different regions of this area. Although such differentiation has not yet been achieved with electrolytic lesions, this may be attributed to use of bilateral techniques. There is error involved in the attempt to produce any lesion by the stereotaxic method. The instrument itself is not perfectly accurate, and the brain of a subject can never model precisely the coordinates found in a stereotaxic atlas.

With bilateral lesions, errors in placement are further compounded, and the resulting lesions are seldom, if ever, identical in size or symmetrical in placement. Therefore it appears reasonable that if the feeding, drinking and finickiness "centers" of the LH can be separated electrolytically, a

unilateral lesioning technique would facilitate such a demonstration. The following experiment was designed to further study the recovery of animals with lateral hypothalamic lesions by placing a unilateral lesion in the LH. Such unilateral lesions should produce brief loss of feeding and drinking and allow more recovery from the feeding and drinking deficits manifested in the lateral hypothalamic syndrome.

METHOD

Subjects

The subjects in this experiment were 38 female albino rats (Charles River Breeding Laboratories, Wilmington, Mass.) approximately 120 days old and weighing 300-350 grams at the beginning of the experiment. They were housed in individual wire cages and maintained ad lib. on tap water in calibrated glass founts (Wahman, Baltimore, Md.) and Purina Rat Chow scattered on the floor. A 12-hour day - 12-hour night cycle was maintained. The colony room was kept at a temperature of about 20-25° C.

Procedure

The animals were handled, weighed, and given fresh food and water daily for a week. After they reached a stable food and water intake, four tests of regulation were administered with three days elapsing between each test. After all tests were completed, unilateral LH lesions were made in each experimental animal. Animals which were completely aphagic to food pellets following surgery were offered chocolate in small glass dishes. As soon as the animals entered Stage IV of the lateral hypothalamic syndrome, the tests were repeated. Tests were repeated subsequently at intervals of approximately one month. Testing was continued for at least three months after the lesion was

made. One subgroup was tested four months after lesioning. At the conclusion of all testing, animals were sacrificed and their brains were examined to determine the extent and placement of the unilateral lesions.

Testing. Four tests were conducted: The first measured the response to hypoglycemia induced by subcutaneous injection of 8 units of crystalline insulin (Lilly). Five animals initially were tested twice with 16 units of protamine zinc insulin. Food and water intake were measured over six hours following the injection of insulin. In the second test, the response to intraperitoneal injection of 1 ml. of 1 M NaCl per 100 gm. of body weight was measured. Water intake in three hours following saline injection was taken. No food was given during this test. In the third test, the water intake of animals was measured over 24 hours of food deprivation. The fourth test measured intake of a 0.08% or a 0.008% w/v solution of quinine hydrochloride over one or two days.

The saline and insulin tests were run during daylight hours. The saline test was ordinarily conducted first in the series of four tests. It was generally followed by the quinine or the insulin test. The water intake over 24 hours of food deprivation was taken last in the sequence. There was always a period of three days between successive tests.

Surgery and histology. The animals were divided into three groups -- one experimental and two control groups. The 19 experimental animals were further divided into three subgroups (indicated by prefix A, B, or C). Ten of the experimental animals received unilateral lesions in the right lateral area of the hypothalamus. The remaining nine received similar lesions on the left side. The side of the lesion was varied during successive operations.

The animal was anesthetized with Equithesin (0.30 ml./100 gm. body weight, Jensen-Salisbury, Kansas City, Mo.) after pretreatment with 0.02 mg. of atropine sulfate. The electrode was inserted perpendicular to the plane of the frontal bones using a Kopf stereotaxic instrument. Coordinates were: 2.5 mm. behind bregma in 9 animals and 3.0 mm. behind bregma in 10 animals, 2.0 mm. left or right of the midsagittal sinus, and 7.5 mm. down from the dura (A: -2.5 or -3.0, L: 2.0, V: -7.5). A lesion was made using 2 ma. d.c. anodal current for a duration of 20 seconds. Electrodes of platinum alloy (90% platinum and 10% iridium, 0.308 mm. [0.012 in.] in diameter) were insulated with Formvar enamel (General Electric, Schenectady, New York) except for a cross-section of the tip.

After the lesion was made, the opening in the skull was covered with a pad of Gelfoam (Upjohn, Kalamazoo). A small

quantity of sulfathiazole powder (Lilly, Indianapolis) was applied over the Gelfoam. Tetracycline (2.5 mg.) was injected subcutaneously at the conclusion of surgery.

One control group of nine animals (sham lesion group, Group F) underwent the same procedure as the experimental rats, except that during surgery the electrode was inserted 5.5 mm. below dura and then removed without lesioning. A third group of ten rats (unoperated group, Group E) did not undergo surgery but was tested repeatedly in the same manner as the other groups.

Following the conclusion of testing, the experimental subjects were sacrificed with an overdose of Equithesin and perfused with normal saline followed by 10% formalin. Their brains were removed, embedded in celloidin and sectioned coronally at 40 micra. Every second section was stained with thionin and was mounted for examination. The lesions were examined microscopically and compared to the atlas of König and Klippel (1963).

RESULTS

Results of Tests of Regulation

Data treatment. A t-value was computed for the difference between the mean of each of the first series of tests of regulation and the mean of each subsequent test. This t-value was calculated for correlated means. Other t-values, for independent means, were computed for the difference between the means of the first series of tests on control groups and the means for pre-lesion tests on the experimental group. Finally, a t-value for independent means was calculated between post-lesion tests on experimental animals and the appropriate repeated test on control animals. For example, the results of post-lesion test 2 (third test given) were compared to the results of test 3 on Group E. A significance level of .10 was used to determine significance. For each test, the difference due to the experimental treatment was expected to be in a decreasing direction.

Hereafter, the tests will be referred to as follows: Each initial regulatory test for the experimental animals will be called "Pre-Test". Tests conducted following lesioning will be entitled "Post-Test" and the number of the Post-Test will be given (e.g., Post-Test 1 will refer to the first test conducted upon the experimental animals following the surgical procedure). Every test on control animals will be designated as Test 1, 2

or 3 depending upon its position in the sequence of repeated tests.

Saline test. The data from the saline tests are shown in Table 1. The results of the t-tests are indicated in Table 1A. The number of animals tested, their mean water intakes, and the ranges of intakes are presented in Table 1B. A drinking deficit was evident for the experimental animals following surgery. It lasted for about three months, at which time recovery seemed to occur.

The means of the three Post-Tests performed on the experimental animals (Groups A, B and C) were significantly less than their pre-lesion mean. The A group (five animals) was tested a fourth time four months following surgery. This mean did not differ significantly from the Pre-Test mean for that group.

The Pre-Test mean was not significantly different from the mean of the initial test on either control group. The means of the second tests on both control groups (Groups E and F) were found to be significantly greater than the mean of Post-Test 1. The mean of Test 3 on the E group (unoperated control) was not significantly different from that for Post-Test 2. No significant difference appeared between the means of Test 1 and Test 3 for the E group. The mean of Test 2 on the F group (sham-lesion control) was significantly greater than that for Test 1 on this group.

TABLE 1

A. Results of t-tests applied to experimental (Groups A, B, and C) unoperated control (Group E) and sham-lesion control (Group F) group means for each saline test conducted.

	(A,B,C) Post-Test 1	(A,B,C) Post-Test 2	(A,B,C) Post-Test 3	(A) Post-Test 4	(E) Test 1	(F) Test 1
Pre-Test(ABC)	.01	.05	.10	--	N.S.	N.S.
Pre-Test (A)	--	--	--	N.S.	--	--
Test 2 (E)	.005 +	--	--	--	.025 +	--
Test 3 (E)	--	N.S.	--	--	N.S.	--
Test 2 (F)	.01 +	--	--	--	--	.10 +

B. Numbers of subjects, mean results and ranges of water intakes (in ml.) over the three-hour saline test period.

	(A,B,C) Pre-Test	(A,B,C) Post-Test 1	(A,B,C) Post-Test 2	(A,B,C) Post-Test 3	(A) Post-Test 4
N	19	19	19	19	5
Mean	10.7	7.0	9.6	9.5	9.2
Range	7.0-13.5	0.0-14.5	5.5-15.0	3.0-15.0	7.5-12.0
	(E) Test 1	(E) Test 2	(E) Test 3	(F) Test 1	(F) Test 2
N	10	10	10	9	9
Mean	10.7	12.8	11.2	8.5	10.8
Range	7.5-13.5	9.0-14.5	6.5-17.5	4.5-12.0	5.5-15.5

\+ The mean of the later test is greater

N.S. No significant difference

The data from individual animals were examined also. Of 19 experimental animals, the water intakes of ten decreased 4 ml. or more between the pre-lesion saline test and the first test following surgery. These ten animals drank 6 ml., or less, of water during the three-hour test, and three drank a maximum of 2.5 ml. By the second test following surgery all animals drank at least 5.5 ml.

Insulin test. Table 2A gives the t-test results found for the insulin tests. The number of animals in each group, their mean intakes and their ranges are presented in Table 2B. Certain individual experimental animals decreased their food intakes on the first Post-Test. Subsequent tests showed a general return to pre-lesion intake levels. Group data failed to demonstrate any but a tenuously significant deficit after surgery.

The t-value comparing means for the Pre-Test and the first Post-Test was significant. The Post-Test mean was the smaller of the two. A comparison of the Pre-Test mean with the mean of the second Post-Test was not significant. A significant difference was found between the Pre-Test and the third Post-Test. The means of the second and third Post-Tests, however, were greater than the Pre-Test mean. No significance was obtained by comparing the fourth Post-Test on the A group with its pre-lesion mean.

TABLE 2

A. Results of t-tests applied to experimental (Groups A, B, and C) unoperated control (Group E) and sham-lesion control (Group F) group means for each insulin test conducted.

	(A,B,C) Post-Test 1	(A,B,C) Post-Test 2	(A,B,C) Post-Test 3	(A) Post-Test 4	(E) Test 1	(F) Test 1
		+	+		++	
Pre-Test(ABC)	.10	N.S.	.10	--	.05	N.S.
Pre-Test (A)	--	--	--	N.S.	--	--
Test 2 (E)	N.S.	--	--	--	N.S.	--
Test 3 (E)	--	N.S.	--	--	N.S.	--
Test 2 (F)	N.S.	--	--	--	--	N.S.

B. Numbers of subjects, mean results and ranges of food intakes (in gm.) over the six-hour insulin test period.

	(A,B,C) Pre-Test	(A,B,C) Post-Test 1	(A,B,C) Post-Test 2	(A,B,C) Post-Test 3	(A) Post-Test 4
N	19	19	19	19	5
Mean	6.3	5.2	6.3	7.0	5.4
Range	4.3-9.2	0.0-11.1	2.9-11.0	4.0-14.3	4.2-7.1

	(E) Test 1	(E) Test 2	(E) Test 3	(F) Test 1	(F) Test 2
N	10	10	10	9	8
Mean	5.2	5.6	5.9	6.2	5.9
Range	3.6-7.8	3.6-12.8	4.3-8.6	4.2-8.0	4.1-7.1

+ Post-Test mean is greater

++ Pre-Test mean is greater

N.S. No significant difference

The mean of the Pre-Test was greater than that for either of the initial control group tests (significantly so for the first test on the E group). No other t-value demonstrated a significant change in the results for any of the control group tests, or for a comparison between control and appropriate experimental group tests.

No significant difference was found between the means of the animals tested with protamine zinc or with crystalline insulin. Therefore, these data have been pooled for all the experimental animals.

On the insulin test, six experimental animals reduced their food intake by at least 2 gm. following surgery. Three other lesioned animals, not included elsewhere in the data, died after Post-Test 1. They ate little during the test and would have been part of this group. Of these nine animals, five ate 3.0 gm., or less, when tested post-operatively. All of the experimental animals increased their intakes between Post-Tests 1 and 2 by at least 0.8 gm. and four increased by more than 2 gm.

Quinine test. Data for the quinine tests were analyzed separately according to the concentration of the quinine solution used. Tables 3A and 3B give results using 0.008% w/v quinine solution and Tables 4A and 4B do this for 0.08% quinine. A decrease in intake of each concentration of quinine solution

TABLE 3

A. Results of t-tests applied to experimental (Groups A, B, and C) unoperated control (Group E) and sham-lesion control (Group F) group means for each 0.008% quinine test conducted.

	(A) Post-Test 4	(A) Post-Test 5	(A) Post-Test 6	(B) Post-Test 3	(B) Post-Test 4	(B) Post-Test 5
Pre-Test(A)	.005	.025	.025	--	--	--
Pre-Test(AC)	--	--	--	.10	N.S.	N.S.

	(C) Post-Test 1	(C) Post-Test 2	(C) Post-Test 3	(E) Test 1	(F) Test 1
Pre-Test(A)	--	--	--	N.S.	N.S.
Pre-Test (C)	.10	.10	N.S.	N.S.	N.S.
Test 2(E)	.025 +	--	--	N.S.	--
Test 3(E)	--	.05 +	--	N.S.	--
Test 2(F)	.005 +	--	--	--	N.S.

B. Numbers of subjects, mean results and ranges of intakes (in ml.) of 0.008% solutions of quinine hydrochloride over 24-hour test periods.

	(A,C) Pre-Test	(C) Post-Test 1	(C) Post-Test 2	(C) Post-Test 3	(A) Post-Test 4
N	12	7	7	7	5
Mean	23.1	16.4	17.8	16.3	17.5
Range	12.8-31.0	3.0-27.0	2.0-27.0	2.0-23.0	15.3-19.8

	(A) Post-Test 5	(A) Post-Test 6	(B) Post-Test 3	(B) Post-Test 4	(B) Post-Test 5
N	5	5	7	7	7
Mean	18.3	18.4	20.6	20.7	20.6
Range	16.8-20.8	15.0-21.5	17.3-22.0	16.8-23.0	13.5-25.5

	(E) Test 1	(E) Test 2	(E) Test 3	(F) Test 1	(F) Test 2
N	10	10	10	9	9
Mean	25.5	25.5	25.1	32.2	35.6
Range	15.0-56.5	15.0-43.0	16.5-33.0	6.0-85.0	21.0-58.0

+ The mean of the control test is greater

N.S. No significant difference

TABLE 4

A. Results of t-tests applied to experimental (Groups A, B, and C) unoperated control (Group E) and sham-lesion control (Group F) group means for each 0.08% quinine test conducted.

	(A) Post-Test 1	(A) Post-Test 2	(A) Post-Test 3	(A) Post-Test 7
Pre-Test (B)	.05	.01	.01	.05

	(B) Post-Test 1	(B) Post-Test 2	(B) Post-Test 6
Pre-Test (B)	.10	.05	N.S.

B. Numbers of subjects, mean results and ranges of intakes (in ml.) of 0.08% solutions of quinine hydrochloride over 24-hour test periods.

	(B) Pre-Test	(A) Post-Test 1	(A) Post-Test 2	(A) Post-Test 3	(A) Post-Test 7
N	7	5	5	5	5
Mean	16.3	5.7	3.0	3.2	6.9
Range	6.8-39.0	3.3-9.5	2.8-3.3	2.0-4.8	3.0-14.0

	(B) Post-Test 1	(B) Post-Test 2	(B) Post-Test 6
N	7	7	7
Mean	11.1	5.3	9.2
Range	2.8-21.3	2.3-9.3	2.0-36.0

N.S. No significant difference

was found following placement of the lesion. This deficit continued for a period of at least three months after surgery.

The Pre-Test on Group A, Post-Tests 4, 5 and 6 for Group A, the third, fourth and fifth Post-Tests on Group B, and all tests for Group C were performed using 0.008% solutions of quinine. All control animals were tested throughout the experiment with this concentration of quinine. The Pre-Test on Group B was conducted using 0.08% quinine. The first, second, third and seventh Post-Tests on the A group and the first, second and sixth Post-Tests of Group B were also done with 0.08% quinine solutions.

For 0.008% quinine, the t-test comparisons for the A group alone all were significant. A comparison of Post-Test 3 on Group B with the Pre-Test mean for Groups A and C was significant, but those comparing the fourth and fifth Post-Tests were not. For the C group, the first two Post-Test means were significantly different from the Pre-Test mean. No such difference was found by comparing Post-Test 3 with the Pre-Test quinine data. In all cases the mean of every Post-Test was smaller than that for the Pre-Test. The first test on control groups was found not to differ significantly from either the Pre-Tests on Groups A and C or from the subsequent control tests. The means of Post-Tests 1 and 2 were found to be significantly larger than

means for control Tests 2 and 3 on Group E and Test 2 on Group F.

For 0.08% quinine, the means of the first and second Post-Tests on Group B were significantly smaller than was the Pre-Test mean for this group. No significant differences were discovered by comparing the sixth Post-Test on the B group with its Pre-Test. All comparisons between the Pre-Test on Group B and every A group Post-Test performed using 0.08% quinine were significant.

A two-day test was performed whenever a 0.08% quinine solution was used. The data from the successive days were summed and divided by two to give a mean 24-hour intake measure. Although t-tests were performed for the intakes on each day of each test, none of the results seemed to warrant separate treatment. They did not demonstrate any differences from the results of tests on pooled data.

Every animal in the A group substantially decreased its intake of 0.008% quinine solution following unilateral lesions. By the fourth Post-Test each still showed a decrease of at least 5 ml., as compared with the results of the Pre-Test for this group. Three animals in the B group dropped at least 8 ml. between their first two tests using a 0.08% solution of quinine. Four of the seven animals in Group C also appreciably decreased their intakes of a 0.008% quinine solution. They drank at least

5 ml. less during the first Post-Test. One animal reduced its intake by 19 ml. Nine of the experimental animals appeared to maintain these drinking deficits in their last test.

Water without food test. Table 5 presents the data from this test. A substantial decrease in water intake was seen in every experimental animal following surgery. All post-lesion tests of water intake over 24-hour food deprivation gave means which were significantly smaller than the Pre-Test means (Table 5A). The Pre-Test mean was not significantly different from either initial control test. A notable decrease in intake was seen for successive tests on the normal control group. The t-tests performed between the means of Tests 1 and 2, and the means of Tests 1 and 3 on Group E, were significant. The first test mean was greater than either of the next two. The first post-operative mean on the experimental animals also significantly differed from Test 2 for Group E. In this case, however, the experimental group mean was smaller. No significant differences were found by comparing Test 2 on Group F or Test 3 (Group E) with Post-Tests 1 and 2 respectively. A t-value comparing Tests 1 and 2 on Group F was also insignificant.

Every experimental animal demonstrated a large deficit following lesioning (at least 13 ml.). The average decrease was 25 ml. No animal ever reached the level of water intake found

TABLE 5

A. Results of t-tests applied to experimental (Groups A, B and C) unoperated control (Group E) and sham-lesion control (Group F) group means for each test of water intake under food deprivation conducted.

	(ABC) Post-Test 1	(ABC) Post-Test 2	(ABC) Post-Test 3	(AB) Post-Test 4	(A) Post-Test 5
Pre-Test (ABC)	.005	.005	.005	--	--
Pre-Test(AB)	--	--	--	.005	--
Pre-Test(A)	--	--	--	--	.025
Test 2(E)	.05 +	--	--	--	--
Test 3(E)	--	N S.	--	--	--
Test 2(F)	N.S.	--	--	--	--

	(E) Test 1	(F) Test 1
Pre-Test(ABC)	N.S.	N.S.
Test 2(E)	.005 ++	--
Test 3(E)	.005 ++	--
Test 2(F)	--	N.S.

B. Numbers of subjects, mean results and ranges of water intakes (in ml.) over 24-hour test periods under food deprivation.

	(ABC) Pre-Test	(ABC) Post-Test 1	(ABC) Post-Test 2	(ABC) Post-Test 3	(AB) Post-Test 4	(A) Post-Test 5
N	19	19	19	19	12	5
Mean	39.2	13.8	13.7	10.3	11.6	13.3
Range	21.5-70.0	2.0-31.5	1.0-44.0	1.5-20.0	4.0-18.0	8.5-24.5

	(E) Test 1	(E) Test 2	(E) Test 3	(F) Test 1	(F) Test 2
N	10	10	10	9	8
Mean	36.8	23.2	18.7	35.4	27.4
Range	15.5-83.0	10.0-42.0	7.5-37.0	7.0-80.0	4.5-95.0

+ The mean of the control test is greater

++ The mean of Test 1 is greater

N.S. No significant difference

in the pre-lesion test. By the third test, one E group control animal surpassed its Test 1 intake level. Two F group animals did so on their second test. The mean decrease between control Tests 1 and 2 was 10.8 ml. Seven of 18 control animals, demonstrated a thirst deficit of 13 ml. or more between Test 1 and Test 2.

Other Observations

Aphagia and adipsia. The experimental animals were closely observed following surgery. Food and water intakes were recorded daily until each subject was eating and drinking at a level equal to at least 50% of its daily intake before the lesion.

The number of days of aphagia (1 gm. or less of dry food eaten in a 24-hour period), adipsia (2 ml. or less water intake over 24 hours), anorexia (less than 50% of pre-lesion daily food intake, including aphagia), and hypodipsia (less than 50% of pre-lesion daily water intake, including adipsia) was recorded for each animal. Only four animals showed more than two days of aphagia. The longest period of aphagia was eight days. The group mean was 1.5 days. Two animals were adipsic for more than 2 days. The longest duration of adipsia was 5 days and the mean was 0.63 days. Ten animals were aphagic for one or more days following recovery from adipsia. Just one was adipsic beyond recovery from aphagia. Six animals remained anorexic

beyond 5 days following surgery. Two were anorexic as late as the fourteenth day after lesioning (group mean = 5.0 days). Six animals (five of which were also anorexic) remained hypodipsic for more than 5 days after surgery. The longest period of hypodipsia was 11 days (group mean = 3.9 days).

A Pearson product-moment coefficient of correlation was calculated for the lengths of aphagia and adipsia ($r = .501$, $p < .05$) and for the lengths of anorexia and hypodipsia ($r = .890$, $p < .01$) for these animals. Percentage change in intake of water and food was calculated between the first Post-Tests and the Pre-Tests of both saline and insulin. A correlation was determined for the length of anorexia and the percentage change in food intake on the insulin test. Another correlation compared the length of adipsia with the percentage change in water intake for the saline test. Both correlations were small and neither approached significance. A Pearson correlation coefficient was also calculated for these percentage changes on the saline and insulin tests. The correlation was again small and insignificant.

Additional lesion effects. In addition to the failure to eat or drink, certain other behavioral changes were observed in the experimental animals after surgery. Twelve subjects showed gastro-intestinal disturbances with diarrhea and intestinal

bleeding that continued for as long as 20 days after surgery. Six animals failed to groom themselves adequately for extended periods of time (6 days or more). They allowed blood, chocolate and fecal material to become matted in their fur and appeared to make no attempt to remove them. The majority of animals had a reddish, watery discharge from their eyes. This was seen frequently on their snouts and on the water tubes, and was observed for up to two weeks in some animals. A marked docility was also noted in several of the animals following surgery. They no longer resisted being lifted, nor did they try to bite or seize objects (e.g., fingers) dangled near them.

Of the animals characterized as most severely deficient in their ability to monitor food or water needs (as demonstrated by their failure to compensate in the initial post-lesion saline or insulin tests), eleven, of thirteen, also showed grooming change, eye discharge, and/or gastro-intestinal problems. Two of the three animals that had both saline and insulin deficits, also experienced extended periods of such difficulties (intestinal bleeding and diarrhea on the fifteenth or eighteenth day after surgery).

Histology

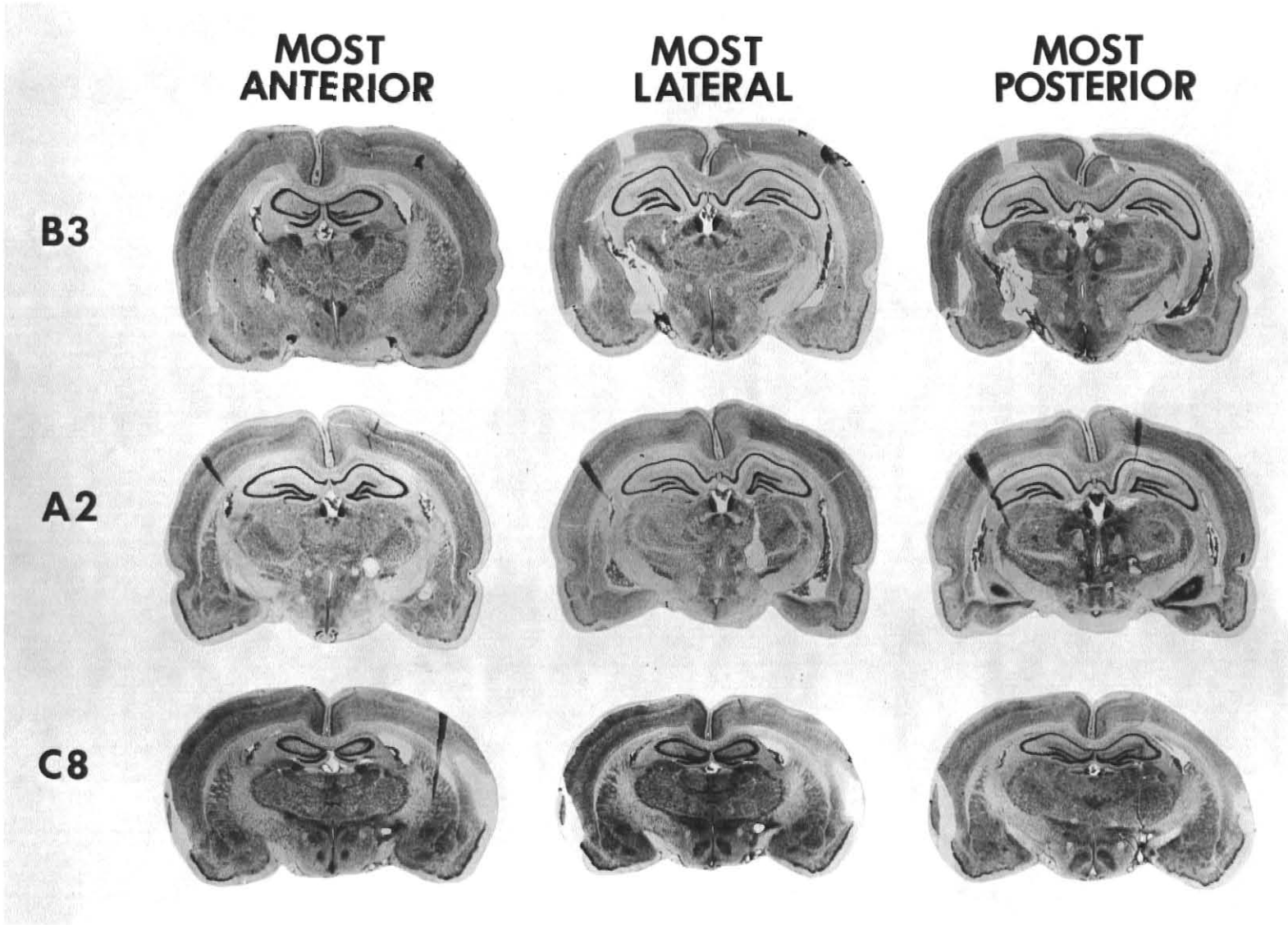
Histological examination was conducted by the investigator without prior knowledge of behavioral results. All lesions

were found to be acceptable and no signs of infection were detected. All animals experienced at least a minimal amount of damage to one side of the LH with some sustaining extensive unilateral LH damage. There was at least some damage to the median forebrain bundle in all cases. Most of the lesions lay in the dorsal half of the posterior part of the LH area (Kőnig and Klippel, 1963). All lesions began behind the posterior border of the anterior hypothalamic nucleus. Many extended to the anterior border of the mamillary complex. Minimal damage, due to the electrode track, was noted through the corpus callosum and the hippocampus.

Six lesions invaded the internal capsule (animals A1, A8, B2, B3, C5, C9). Only one of these (B3), the largest of all the lesions, produced any extensive damage to this structure. This lesion also invaded a portion of the medial amygdala and the stria terminalis. One animal (A2) sustained minimal LH damage. Its lesion was dorsal and extended into the medial lemniscus. As the lesion was traced posteriorly, it extended into the zona incerta just dorsomedial to the substantia nigra and just lateral to the fornix. Figure 1 shows the most anterior, lateral and posterior extents of the largest (B3), smallest (A2) and best-placed (C8) lesions. The lesion in C8 is representative of the majority of the lesions. It is well-placed within the

Figure Caption

Fig. 1. The most anterior, lateral and posterior extents of each of three unilateral LH lesions are shown. The first animal, B3, sustained the largest lesion. Animal A2 showed the most minimal LH damage. The third animal, C8, had a lesion representative in size and location of the majority of the experimental animals.


MOST ANTERIOR
MOST LATERAL
MOST POSTERIOR
B3
A2
C8

lateral area and is approximately the same size as, or slightly smaller than, most of the lesions.

The most dorsally-located lesion (B1) invaded a part of the medialis dorsalis and a larger area of the lateral thalamic nucleus. This damage appeared to have resulted from a gap in the insulation on the electrode. The most ventral damage was made by a lesion (C4) extending to the base of the ventral surface of the brain. This lesion encroached upon the most medial aspect of the optic tract.

No reliable relationships between size or placement of lesion and between behavioral deficits are apparent. In attempting to compare the animals most severely affected on the saline and insulin tests, with the histological data, no correlation was evident. Animals with either, or both, deficits sustained lesions that did not appear to overlap in any particular area. Their lesions were in the dorsal, ventral or lateral parts of the LH and neither size nor location could be used to predict behavioral change. Since the electrode penetration that produced the more ventral lesions must have passed through the dorsal aspect of the LH, it is possible that such minor damage could have been responsible for the subsequent behavioral deficits.

The variation in placement of the electrode posterior to bregma (-2.5 or -3.0 mm.) also appeared to have no differential effect. Three animals showing a severe deficit in the insulin test had placements at 2.5 mm. and three were 3.0 mm. behind bregma. Six of the animals deficient on the saline test had placements at -2.5 mm. and the other four were at 3.0 mm. posterior to bregma. These deficient animals were also equally divided as to whether the electrode was placed in the left or right half of the hypothalamus.

DISCUSSION

Animals with unilateral LH lesions show clear physiological deficits. Their ability to respond on tests of regulation was partially or totally disrupted. Recovery from these deficits of behavioral regulation varied, depending upon which test of regulation is considered.

The *t*-tests applied to group data from the saline test show a reliable drop in water intake following unilateral lesions. Although a fourth post-lesion saline test was performed only upon a sub-group of five animals (Group *A*), the failure to find significance four months after the lesions were made implies that recovery has occurred. Recovery of the ability to compensate for hyperosmolarity produced by hypertonic saline injection takes place approximately three months following a unilateral LH lesion.

The results of the insulin tests are less clear. The Pre-Test mean for the experimental group was larger than the initial mean found for the unoperated control group. Thus, the reliability of the significant *t*-test result between the Pre-Test and the first test after lesioning may be questioned. On the other hand, there is only a small difference between the means of successive control tests, while a significant decrease exists between the Pre-Test and Post-Test 1 on the experimental animals.

No other tests demonstrated significant decreases for any of the groups. Therefore, an insulin effect occurred, but a definitive statement cannot be made from these data.

It was noted, on the initial post-lesion insulin test, that six of the 19 experimental animals reduced their food intakes substantially below their pre-lesion levels. Those six also demonstrated considerable recovery between Post-Tests 1 and 2. Three other animals died shortly after the first Post-Test because they did not eat enough to compensate for insulin-induced hypoglycemia. Thus, it does appear that a unilateral LH lesion can affect the ability to regulate blood glucose. Apparently, only nine lesion placements, out of 22, intruded upon the appropriate hypothalamic "center". By pooling the data from all the experimental animals, the individual effects of such lesions were obliterated.

The quinine test data indicate that animals are finicky after a unilateral LH lesion. That is, the threshold for aversion is significantly lower. Tests performed using a 0.08% quinine solution produced a marked decrease in fluid intake with or without a lesion. As a consequence, only a further, large decrease in intake by the majority of the animals could produce differences which would be significant. This lends added credence to the significant *t*-test results found with 0.08%

quinine -- those comparing the first two post-lesion B group test means with this group's pre-lesion result, and all Post-Test comparisons for Group A. Tests using 0.008% quinine were equally sensitive to this deficiency. Six of the nine tests comparing pre- and post-lesion data, using this concentration, gave significant t-test results.

It has already been mentioned that every member of the A group was found to be severely deficient on the quinine test. Only seven of the twelve animals in the other experimental groups were similarly deficient. Recovery seems to have occurred in the B and C groups by about three months after surgery. No recovery is apparent in the A group data. Because of the universal deficiency found in the A group, the best indication of the effects of a unilateral LH lesion should be sought here. Since the animals that showed a severe initial deficit continued to do so throughout testing, this strongly suggests that recovery does not take place. Just three animals showed any evidence of recovery at the conclusion of testing. The failure to find continued significant differences for the Post-Test results of the other groups could be due to the increased intakes of animals relatively unaffected by the lesion. As with insulin, pooling the data may obscure the actual effects of the lesion.

Repeated tests of water intake during 24-hour food deprivation produced decreases in the water intake of Group E animals. No comparable decrease was discovered between the two tests on Group F. Six of the eight animals in Group F did drink appreciably less during their second test. Two members of this group, however, increased their intake to such an extent that the variance for the group became quite large and averted any statistical significance. This may explain the failure to find significant differences by comparing Post-Test 1 on the experimental animals with Test 2 on the F group. The means for these tests were dissimilar, but the variance in the F group was large.

Although experience is a factor in the decreased water intake found for these animals, the experimental treatment cannot be discounted. The mean of the second test on Group E was significantly larger than that for the first Post-Test on the experimental animals. Thus the lesion must account for part of the deficit.

Since the mean of the third control test (for the test of water with food deprivation) showed a further decrease, it is probable that the added effect of experience eliminated any difference that still existed between the experimental and control animals. The mean water intakes were quite low for almost all the animals at that point. Possibly, a 48-hour test could

be used to better segregate a lesion effect from the effect of experience in such a circumstance. No conclusions can be drawn concerning recovery from this drinking deficit until the effect of repeated testing is better analyzed.

The results of these four tests emphasize the presence of distinct physiological deficits following unilateral LH lesions. They also indicate that the severe homeostatic deficiencies -- those related to the inability to respond on the saline and insulin tests -- are transient when compared to the continued finickiness and failure to drink. Recovery of glucoregulation appeared in all animals within a month. Recovery of osmoregulation took place within three months.

The prolonged increase in aversion to solutions of quinine and the continued failure to drink when deprived of food appear to represent the same phenomenon of finickiness. The failure to drink when deprived of food could be explained either as a lowered threshold for aversion or as an increased threshold for thirst. The taste, consistency or tactile sensations occurring during drinking may assume noxious characteristics for the animal. Just as the animals shows increased aversion to the taste of quinine, it also may find water unpalatable. Thus, the animal is a prandial drinker, responding only when mouth dryness overcomes water aversion. Alternatively, after a unilateral LH

lesion the sensations used to monitor thirst (e.g., oropharyngeal dryness, increased tonicity, etc.) must be stronger in order for water need to be recognized, and corrected, by the animal. Nevertheless, an aversion to water still could operate to produce a lowered intake in the absence of food since oropharyngeal dryness would be less.

Since animals were found which were deficient on some, but not all, of the tests, it appears that a unilateral lesion can differentially affect different regulatory centers for feeding and drinking, and centers for taste factors in the LH. Although there is no reliable histological evidence to support this conclusion, the behavioral results do provide a basis for such a statement. If the lesions had been smaller it might have been possible to isolate these centers more accurately histologically. Since the lesion produced pervasive finickiness, the entire LH area may be considered as involved in the control or maintenance of thresholds of aversion. Damage anywhere in this area results in increased aversiveness. The idea of a highly-specific finickiness "center" appears unreasonable in light of this evidence.

It has been proposed that when adipsia and aphagia occur in an animal with bilateral LH lesions, the adipsia is the more persistent deficit (Teitelbaum and Epstein, 1962). In Stage III of the "lateral hypothalamic syndrome", an animal regulates

caloric intake with dry food but will not drink water. The results of the present study are opposite to this evidence: adipsia and hypodipsia were less severe in comparison with the deficits in feeding. Ten animals, of 13 showing aphagia, began drinking water (Stage IV) before they ate dry food (Stage III). Unilateral LH lesions can produce either more severe drinking or more severe feeding deficits.

The length of aphagia and the length of adipsia are significantly correlated, as are the lengths of anorexia and hypodipsia. The severity of these initial deficits, however, does not predict any corresponding loss of regulation with regard to hypoglycemia and hypertonicity (insulin and saline tests). The mechanisms responsible for thirst and hunger do not appear to be related strongly to those responsible for regulating other types of homeostatic balance. One regulatory behavior may appear before another. The ability of a lesioned animal to respond to changes in blood tonicity may recover relatively rapidly following a lesion. The physiological response to oropharyngeal sensations may not return as soon. If the rates of recovery in separate systems are unrelated, then there would be no need to assume that any correspondence must exist between deficits in feeding and drinking and deficits in specific tests of regulation.

The process of encephalization in infancy appears to parallel recovery from the lateral hypothalamic syndrome (Teitelbaum, Cheng and Rozin, 1969). Weanling rats, retarded in development by thyroidectomy on the first or second day of life, undergo an orderly sequence of stages of development of feeding and drinking behaviors. Although initially adipsic and aphagic, they begin eating highly palatable foods. This is followed by regulation of feeding without water drinking. Eventually the animals appear to eat and drink normally. Other physiological deficits (like Stage IV) are seen. Finally full regulation of hunger and thirst is evident.

Although this process of encephalization does illustrate many of the phenomena seen with recovering lateral animals, the observation in the present study that aphagia does not always disappear prior to the disappearance of adipsia must not be discounted. This is at least one part of the unilateral syndrome that fails to parallel results found with tests on developing neonates or on recovered bilateral animals.

The process of recovery may be considered as essentially a process of re-encephalization of function. Teitelbaum and Epstein (1962) repeatedly lesioned animals that had recovered to Stage IV of the lateral hypothalamic syndrome. Aphagia and adipsia reappeared in relesioned animals. Teitelbaum and

Cytawa (1965) supported the concept of re-encephalization by producing functional decortification (spreading depression) in rats that had previously recovered from LH lesions. Such treatment reinstated aphagia and adipsia once more. Wampler and Teitelbaum (1966) showed that unilateral LH lesions impair self-stimulation on both sides. They suggest that a "shock" phenomenon, caused by the disruption of facilitatory input from each half of the lateral hypothalamus to the other, results in immediate depression on the intact side.

The additional lesion effects observed (grooming deficit, gastro-intestinal difficulties and eye discharge) resemble those noted by Teitelbaum and Epstein (1962) in their discussion of animals with bilateral LH lesions. Docility, poor grooming, etc. are characteristic of animals in Stage I of the lateral hypothalamic syndrome. The appearance of the animals following unilateral LH lesions emphasizes the similarity of the effects of bilateral and unilateral damage to the LH. Although unilateral lesions result in short-term, less severe deficits, the effects of unilateral lesions parallel closely those of bilateral ones.

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RECOVERY OF SPECIFIC DEFICITS FOLLOWING UNILATERAL LESIONS OF THE LATERAL HYPOTHALAMUS IN RATS

by

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Unilateral lesions of the lateral hypothalamus were made in 19 female albino rats. Following placement of the lesion, the animals were given a series of four tests: response to hyperosmolarity produced by an injection of hypertonic saline solution, response to insulin-induced hypoglycemia, 24-hour intake of quinine solution and 24-hour intake of water during food deprivation. The results showed deficits on all the tests following unilateral lesions. Post-lesion saline tests demonstrated a reliable decrease in water intake. Recovery from this deficit appeared to occur within three months. Individual animals were found to decrease their food intake on post-operative insulin tests. Recovery of glucose regulation occurred in all animals within one month. Quinine test results indicated that all animals were finicky following the lesion. No substantial evidence of recovery from this deficit was found. Every lesioned animal decreased its water intake on food deprivation. A significant effect of repeated testing was noted here and, as a result, no conclusion could be drawn concerning recovery from this deficiency. Although unilateral lesions result in short-term, less severe deficits, the effects of unilateral lesions parallel closely those of bilateral lesions.