EXPERIMENTAL HYPOTHALAMIC HYPERPHAGIA IN THE ALBINO RAT*

JOHN R. BROBECK, JAY TEPPERMAN, AND C. N. H. LONG

Introduction

Experimental study of hypothalamic obesity is based upon a foundation laid by clinicians who described lesions of the hypophysio-hypothalamic region in obese human patients. Because of the non-specific character of the lesions which they found, previous investigation was naturally directed toward discovering whether damage to the hypothalamus, to the hypophysis, or to both was necessary to produce this condition. A brief review of the data which established the hypothalamic etiology follows.

Hypothalamic obesity was first described by Mohr[42] in a 57-year-old woman who became remarkably obese within the year before her death. At autopsy there was found a hypophysial tumor large enough to deform the sella and to distort and compress the base of the brain, including the cerebral peduncles, optic nerves and chiasma, and the region of the hypothalamus. No attempt was made to explain the excessive deposition of fat nor to distinguish between the hypophysial and the hypothalamic injury.

By the time of publication of Fröhlich's paper[20] in 1901, nine similar reports had already appeared. Fröhlich considered the essential symptoms of the disease to be adiposity and genital underdevelopment caused by pituitary involvement that failed to produce acromegaly. His theory of the hypophysial origin of the condition, although now completely discredited, was supported by the experimental study of Crowe, Cushing, and Homans,[13] Bell,[3] and Dott.[15]

Three years later, Erdheim,[17] in 1904, questioned the validity of Fröhlich's theory, pointing out that in certain cases of this type of obesity the hypophysis had been found to be relatively undamaged, that no particular type of tumor had been found responsible, and

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that compression of the base of the brain was invariably present when adiposity had been noted. Erdheim therefore concluded that a neural lesion produced the condition, although he was not able to identify the structure concerned. His thesis received experimental substantiation when, in 1912, Aschner[1] observed adiposity in dogs subjected to hypophysial operations which were subsequently found to have injured also the infundibulum. Aschner's results were confirmed by Bailey and Bremer[2] and by Camus and Roussy.[11] The matter was considered to be controversial, however, until Smith[57, 58] reported that no obesity followed lesions restricted to the hypophysis of rats, although obesity appeared in rats with concomitant hypophysial and hypothalamic damage. Grafe and Grünthal,[23] Biggart and Alexander,[5] and Hetherington and Ranson[26] more recently confirmed Smith's observations. Hetherington,[25] and Hetherington and Ranson,[27] with the aid of the Horsley-Clarke instrument, produced hypothalamic obesity in rats in which, for the first time, direct hypophysial involvement was avoided. Hetherington and Ranson also reported[28] their success in producing typical hypothalamic obesity in hypophysectomized rats. Their study leads to the conclusion that pituitary damage is important in the etiology of obesity only in so far as it may be one cause of hypothalamic pathology, by pressure or by infiltration with tumor.

Although obesity of this type was known clinically for more than a hundred years and was studied rather extensively for 30 years, no attempt appears to have been made to determine the source of the material deposited as fat. Keller and his collaborators observed transient adiposity in dogs and cats with hypothalamic lesions, and found this to be associated with "enhanced appetite" (Keller, Hare, and D'Amour,[32] Keller and Noble,[33, 34] Keller, Noble, and Hamilton[35]). Their published data are inadequate, however, to prove the general thesis that overeating causes hypothalamic obesity.

On the other hand, certain clinicians studying obesity were genuinely interested in the pathogenesis of the condition. Impressed by early quantitative studies of energy metabolism, physicians like Newburgh,[43] Wilder,[64] and others began to emphasize the importance of overeating in producing hypothalamic obesity as well as other types (see also Greene,[24] Bruch,[10] Rony,[52] Evans[18]). Experimental literature, nevertheless, furnished no acceptable confirmation of their clinical hypotheses.

The present study was undertaken to investigate the pathogenesis of hypothalamic obesity in the rat by measuring the energy exchange of animals subjected to hypothalamic operation.

Materials and methods

Obesity was induced in 200-300 gm. albino rats of the Yale or Sprague-Dawley strains, by making bilateral hypothalamic lesions with the aid of the Horsley-Clarke instrument adapted by Clark[12] for use on the rat. Female rats were used for all experiments except the pancreas protein feeding. Under Evipal anesthesia, electrolytic lesions were made with a direct current of 2 milliamperes for 15 seconds, using a unipolar electrode introduced through a drill hole in each parietal bone. The lesions were always placed in approximately the same location, utilizing coordinates which were found to give effective damage. The following control rats were subjected to operation to produce thalamic lesions: 119, 121, 123, 127, 131, 137, 160, 172, and 174.

Each animal with lesions was compared with a control rat of the same strain, age, and initial weight; they were fed identical diets with the exception of control rats 101, 103, 105, and 107 which were changed to a chow diet while the rats with lesions, 100, 102, 104, and 106, were being used for the food choice experiment reported below. Control rats were given more food than they ate daily. The stock diet fed in unmeasured amounts was "dog chow" pellets (Purina). When food intake was to be measured, the rats were given one of the following: (1) finely ground "dog chow" mixed with an equal weight of water; (2) equal parts by weight of water and "calf meal" (Cooperative G. L. F. Mills, Inc., Buffalo, N. Y.); (3) a mixture of ground fresh lean beef, 2000 gm.; corn meal, 2000 gm.; casein, 1000 gm.; lard, 250 gm.; cod-liver oil, 40 gm.; salt mixture, 5 teaspoonfuls; and water, 1750 ml.; (4) a similar mixed diet in which ground fresh pig liver replaced the beef. Diet 3 or diet 4 was prepared by mixing the ingredients, dividing the mass into portions suitable for a day's feeding, freezing the portions and storing them in the freezer; they were later thawed as needed each day. The rats with hypothalamic lesions apparently gained weight more rapidly on the fresh meat diets than on the commercial preparations; in a few instances rats which had almost ceased gaining on "chow" or "calf meal" began to gain again when a fresh meat diet was provided. In other respects, however, uniform results were obtained with the different diets.

Food intake was measured by weighing the individual food cups on a spring balance before and after they were filled daily. One gram per day was arbitrarily allowed for evaporation of water from wet diets, and an attempt was made to control this factor by giving each animal daily only a gram or two more than it was expected to eat. When spilling of food was noted, the rat was given a larger food cup; if this was ineffective in prevent-

ing spillage, the amount lost was estimated daily or (as in a few paired feeding experiments) the animal was discarded.

Feeding experiments were also conducted with 2 other diets. In the first of these experiments, Sprague-Dawley male rats were fed a diet containing a protein obtained from beef pancreas (White and Sayers[63]) before and after they were subjected to hypothalamic operation; in the second, 4 female rats with lesions were given the components of diet 3 in separate containers, with olive oil substituted for the lard. Food intake was measured daily.

Paired feeding was carried out on 12 pairs of animals by giving the rat with lesions the amount of food consumed by the control on the previous day. Oxygen consumption and respiratory quotients were estimated during 2- to 3-hour periods when the rats had been deprived of food for from 16 to 24 hours. A modified open circuit Haldane apparatus was used.

Discovery of chronic glomerulonephritis at autopsy of rat 34 led to the examination of urine specimens from a group of obese rats and their controls. Albuminuria was estimated qualitatively by the familiar heat and acetic acid test performed on filtered urine collected under toluol; cells and casts were sought microscopically without centrifugation. Sections for microscopic study of the kidneys were prepared by the Masson technic.

Carcasses and viscera were inspected grossly at the time of death or of sacrifice of the animals. In 10 pairs of rats, blood was drawn from the heart for estimation of blood lipid levels; these analyses were carried out in the laboratory of Dr. E. B. Man by the methods of the following: Man and Gildea,[38] Man and Peters,[40] Man and Gildea,[39] and Bogdanovitch and Man.[6] Endocrine organs were weighed in a series of 12 fat and 9 control rats although the glands have not yet been adequately examined microscopically. Brain-stems were removed before fixation in 4 per cent formaldehyde; they were embedded in paraffin, sectioned serially at 10 micra, and stained by Nissl technic for nuclear identification.

Results

Hypothalamic hyperphagia.

Hypothalamic lesions which eventually induced adiposity were found to produce an increase in the amount of food eaten by the rat—an increase which was usually evident even before the animal had completely recovered from the operation. As the effects of the Evipal disappeared many of the animals showed locomotor hyperactivity as described by Hetherington and Ranson,[30] but when food was given to these rats they substituted ravenous eating behavior for the locomotion. They voraciously gnawed and ate chow pellets before their pharyngeal reflexes were sufficiently

re-established to maintain an adequate airway, and at least 3 rats suffered severe acute (and in one case, fatal) dyspnea from inhalation of food particles. The animal which died had distended its stomach, esophagus, and pharynx with chow. Other animals undoubtedly would have died in a similar way, but from the time of this fatality they were not given free access to food until they appeared to be completely recovered from the anesthetic. Even then they usually ate ravenously, but without untoward complication.

Post-operative behavior of the rats may have been influenced by the Evipal, but the hyperphagia and transient locomotor hyperactivity cannot be attributed to the barbiturate because normal animals and rats with control lesions showed no such behavior during recovery from similar anesthetization.

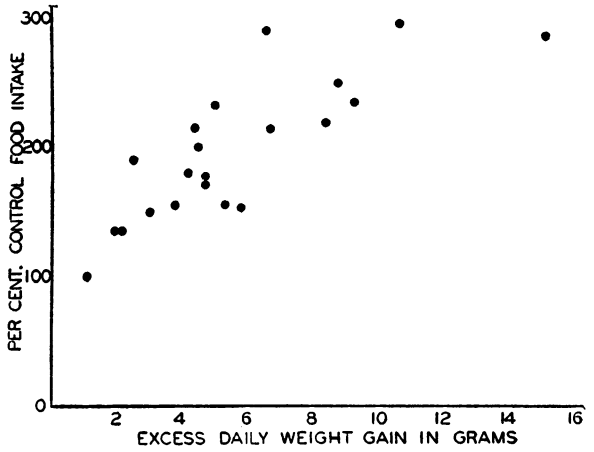


FIG. 1. Correlation between food intake (as percentage of control intake) and weight gain (in excess of control gain) of obese rats. Each point represents one pair of animals.

Because of their voracity the rats increased their body weight by as much as from 20 to 23 grams within the 18 hours following operation. Most of this weight gain undoubtedly represented food in the gut with the water mixed with it. By the end of the first 24-hour post-operative period the hyperphagia was no longer evident on casual inspection, but it was readily proved to be present when the measured food intake of the rats was found to be as much as 3 times the normal daily amount (Table 1). When these rats were relatively restricted by feeding them daily a normal amount of food, they again ate quickly and greedily, consuming in some instances a day's portion in less than an hour.

A definite correlation was found between the rate of weight gain and food intake (Fig. 1). The average daily food intake of each rat with lesions was calculated for the period of most rapid weight gain, and was compared with the average intake of the control animal

(always fed the same diet) during the same period. This comparison is represented in percentage on the ordinate of the graph. The abscissa represents the amount in grams by which the average daily weight gain of the rat with lesions exceeded that of the control rat. The graph shows that the 2 variable quantities are correlated, and the laws of thermodynamics suggest that the relationship is one of cause and effect—that is, food intake determines weight gain.

Data from these experiments are summarized in Table 1, with the number of each rat, the initial and maximal body weights, the maximal rate of weight gain, the length of the period during which this rate was maintained, and the total food intake of that period in percentage of the control intake. ("Maximal weight" or "maximal rate of weight gain" of a control animal is the value observed at the time the obese animal attained its greatest weight or most

TABLE 1

BODY WEIGHT AND RATE OF GAIN

	Weight		*Maximal rate of weight gain*		
Rat No.	*Initial*	*Maximal*	*gm./day*	*Duration (days)*	*Food %*
11	140				
	258	537	5.0	26	215
C1	126				
	250	289	0.6	26	100
20	215	624	2.7	74	*
33	250	570	6.8	22	*
C4	266	385	0.6	34	*
34	244	850	5.5	26	*
C4	266	424	0.6	34	*
35	261	682	5.3	34	*
C4	266	382	0.6	34	*
36	256	582	6.1	22	*
C4	266	390	0.6	34	*
44	195	500	8.7	9	220
C5	210	310	0.3	9	100
52	218	522	6.6	25	290
C11	226	278	0	25	100

* Food intake unmeasured.

TABLE 1 (Continued)

Rat No.	Weight		Maximal rate of weight gain		
	Initial	Maximal	gm./day	Duration (days)	Food %
53	237	522	5.8	26	177
C12	237	285	1.1	26	*
54	222	670	5.5	25	171
C13	254	393	0.8	25	100
69	225	554	6.6	18	*
C68	227				
71	262	572	3.0	16	150
C72	250	371	0	16	100
75	213	526	3.5	28	*
C74	222				
90	264	738	6.7	17	213
C93	242	306	0	17	100
94	254	472	2.8	32	189
C95	250	274	0.3	32	100
98	266	472	3.4	28	136
C99	294	352	1.3	28	100
100	285	568	10.1	12	234
C101	272	316	0.8	12	100
102	305	610	11.5	11	296
C103	271	271	0.8	12	100
104	321	583	9.6	12	249
C105	328	344	0.8	12	100
106	291	593	16.0	6	286
C107	259	300	0.8	6	100
118	204	612	5.5	30	157
C119	200	407	1.7	30	100
120	185	458	2.0	51	*
C121	188	409†	1.1	51	*
122	180	484	4.2	19	100
C123	180	352	3.1	19	100
124	178	385	2.4	37	*
C125	182	326	1.2	37	*

† C121 was the only rat that became obese following "control" lesions; microscopic sections of the brain-stem are not yet available.

TABLE 1 (Concluded)

Rat No.	Weight		Maximal rate of weight gain		
	Initial	Maximal	gm./day	Duration (days)	Food %
126	183	396	4.8	8	135
C127	172	322	2.8	8	100
130	195	518	3.9	18	*
C131	195	318	1.5	18	*
136	229	375	2.8	21	*
C137	235	287	1.1	21	*
144	260	466	5.2	12	180
C143	272	334	1.0	12	100
146	256	456	5.2	22	200
C145	250	282	0.7	22	100
159	291	532	5.6	14	233
C160	258	325	0.6	14	100
171	215	285	3.9	10	155
C172	222	227	—1.4	10	100
173	249	440	7.4	14	154
C174	250	296	1.6	14	100

rapid rate of gain.) The heaviest female rat was number 34, weighing 850 gm. (control weight, 424 gm.), while rat 90 was next heaviest at 738 gm. (control weight, 306 gm.). Other obese rats weighed almost twice as much as their controls. The rate of weight gain was proportionately elevated; rat 106 gained an excess of 15.2 gm./day for a 6-day period, rat 102 outgained its control by 10.7 gm./day for 11 days, and many of the obese rats exceeded the daily average control gain by from 5 to 10 grams for relatively long periods of time. Certain of the rats doubled their own initial weight in 3 months or less (rats 11, 100, and 102); other animals, especially those initially used for paired feeding experiments, gained more slowly but for a longer period of time, attaining their maximal weight only after 10 months or more (rats 34, 54 and 90).

Figure 2 illustrates the course of a typical animal, rat 11, which was the first fat rat studied in these experiments. With respect to food intake and body weight, all similar experiments have confirmed the results of this first experiment. Rat 11 was subjected to 2 operations, the first of which was unsuccessful in that it did not change the level of food intake or rate of weight gain. At the second operation a pair of lesions was placed slightly caudal to the first pair. (The coordinates found to be successful at this second operation were used for preparation of most of the other rats of the series.) Food intake was then found to be greatly increased and a rapid weight gain was noted. When restricted to a normal amount of food, the obese animal slowly lost weight, undoubtedly because of its increased oxygen consumption (see below); but hyperphagia again produced weight gain when the rat was later given larger quantities of food.

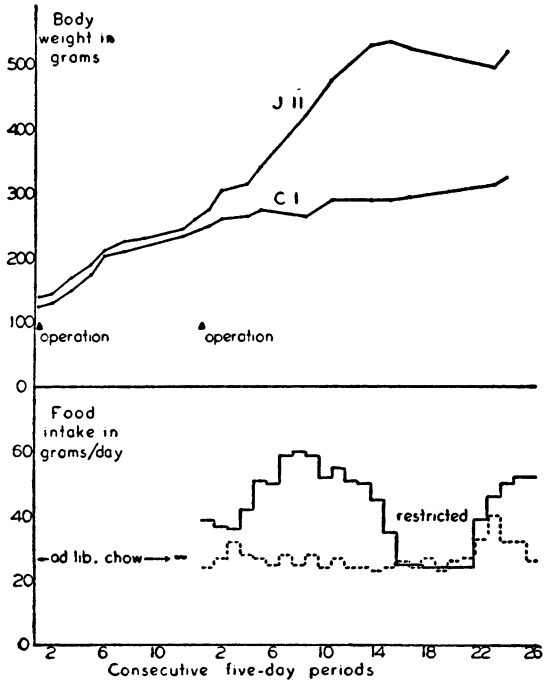


FIG. 2. Food intake and body weight of rats 11 and C1.

Figure 3 compares postoperative hyperphagia with pre-operative food intake in 2 animals; this figure also illustrates a phenomenon which was further investigated, namely, a tendency for hyperphagia gradually to disappear as the rats became obese. This was not caused simply by recovery from the effects of the lesions, for after 6 obese animals with this tendency had been completely fasted to return their weight to normal, they were again hyperphagic and became obese a second time on re-feeding (Fig. 4). The persistent

effect of hypothalamic lesions was also evident in experiments where development of obesity was postponed for several months by the restricted diet of paired feeding experiments (Fig. 7).

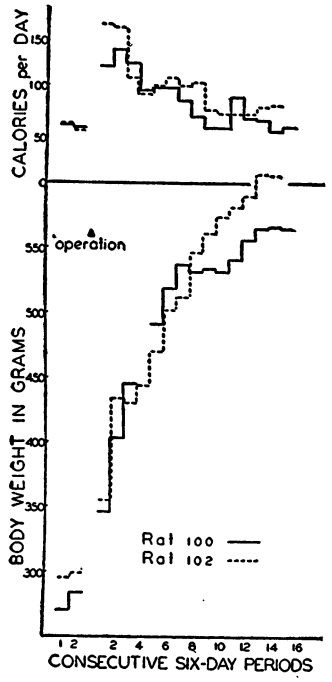


FIG. 3. Average daily caloric intake and body weight of two rats before and after production of hypothalamic lesions.

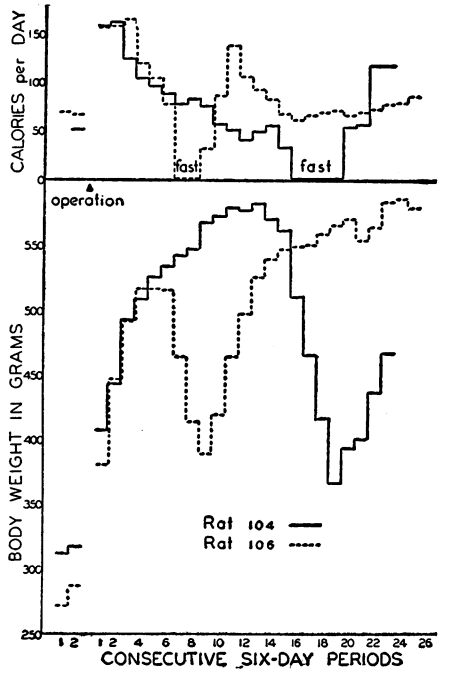


FIG. 4. Effect of prolonged fasting on food intake and body weight of two rats with hypothalamic lesions.

Male rats maintained on the pancreatic protein-containing diet (White and Sayers[63]) became larger than the female rats of the series, but they also exhibited hyperphagia and obesity following the production of hypothalamic lesions (Fig. 5). One of the pancreatic protein fed male rats with lesions attained a weight of 982 grams, and another now weighs 962 grams, while 3 control animals fed the same diet weigh from 600 to 700 grams. Since the giant rats of Benedict, Horst, and Mendel[4] weighed only 766 and 830 grams, the rats of the present series are apparently the heaviest rats thus far observed.*

Paired feeding experiments and determinations of oxygen con-

* These rats were cared for by Mrs. Marion Sayers, in the laboratory of Dr. Abraham White.

sumption indicated that in the rats with lesions, total metabolism was not depressed. Under fasting conditions, oxygen consumption was the same in pair-fed rats with lesions and in control rats. With the body weight gain of *ad lib.* feeding, the total amount of oxygen utilized by each animal increased significantly, proving that a depressed fasting metabolism was not responsible for the progression

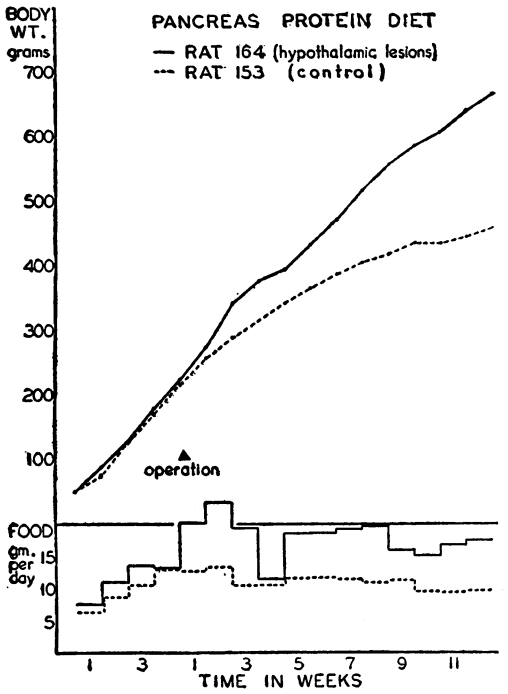


FIG. 5. Hypothalamic hyperphagia in male rat fed a diet containing pancreatic protein.

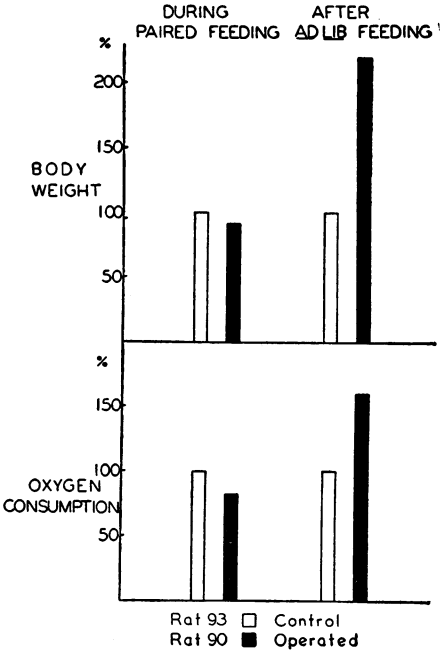


FIG. 6. Fasting resting oxygen consumption of rat 90 before and after the development of obesity.

of the obesity (Fig. 6). In the fasting, resting state the obese rats weighing about 600 grams used approximately twice as much oxygen as did the pair-fed rats with lesions or the control rats weighing about 250 grams. The site of utilization of this excess oxygen is not known, but since the abdominal viscera were generally enlarged (see below), their metabolism may have accounted for at least a portion of this oxygen. On the other hand, animals as large and as heavy as the obese rats would be expected to perform extra muscular work in maintaining posture, respiration, and circulation of the blood.

In 9 out of 12 paired feeding experiments the rat with lesions gained with its control, only to become obese when the former was given larger amounts of food (Fig. 7). Under the conditions of paired feeding the only evident abnormality was habitually rapid eating on the part of the rats with lesions, for they ate a day's portion of food in a relatively few hours. (For discussion of the effects of this type of eating, see Tepperman et al.[61]) In one respect, however, the paired feeding experiments were inconclusive. In 3 pairs of animals the rat with lesions gained more rapidly than the control when they were fed the same amount of food. The occurrence of this disproportionate gain in greatest degree in the animal which ate a day's portion of food in the shortest time (about one hour) suggests that the phenomenon may be related to the feeding habits of the 3 animals in question. This suggestion is supported by the observations of White and Sayers (personal communication) in paired feeding experiments with unoperated rats. They found that a group of rats fed a pancreatic protein-containing diet ate rapidly and gained more weight than a control group which ate at a slower pace an equivalent amount of a casein-containing diet. Feyder[19] evidently observed a similar disproportionate efficiency of food utilization when he compared the effects of feeding a mixed diet containing sucrose with one containing glucose.

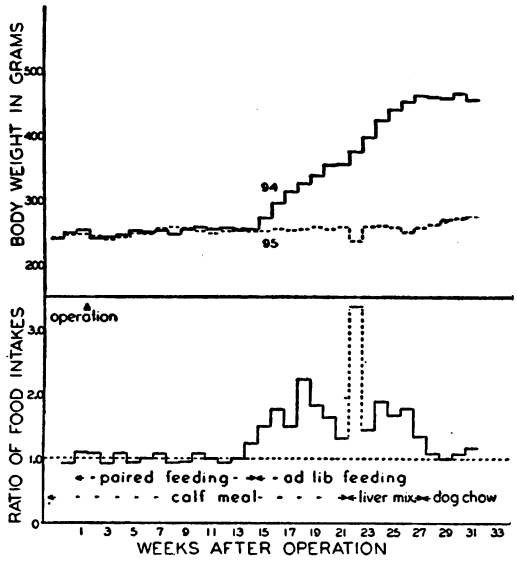


FIG. 7. Effect of paired feeding on weight gain of rat with hypothalamic lesions. This response was observed in 9 out of 12 pairs of animals.

"Self selection" of diet.

Four rats (100, 102, 104, and 106) were subjected to hypothalamic operation after they and their controls had been maintained

for a month in cages where the components of the fresh beef diet were available in separate containers. Since Richter and his associates[47, 48, 50, 51] have found that rats are able to select what are considered to be appropriate dietary elements under a wide variety of experimental conditions, extrapolation of their data suggests that if rats with hypothalamic lesions suffered some particular "metabolic"

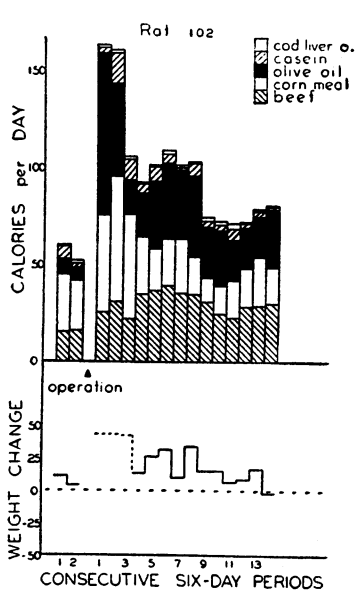


FIG. 8. "Self selection" feeding before and after hypothalamic lesions. Dotted line represents average weight change during 18 days when animal was not weighed.

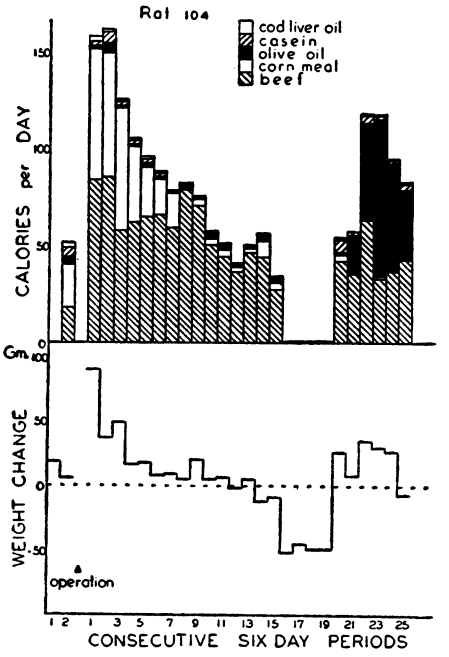


FIG. 9. "Self selection" feeding before and after hypothalamic lesions and after 27-day fast.

deficit, they would choose some particular component or avoid certain types of food. Diets of the 4 rats, however, showed no consistent change in composition after operation, although all of them ate at least twice as much as before. They were evidently able to become obese on carbohydrate, on protein, or on fat (Figs. 8 and 9). They apparently recognized no inability to utilize fat, for rat 102 spontaneously ingested as much as 14.5 ml. of olive oil daily.

Kidney function.

A summary of the albuminuria found in obese rats and in their controls is given in Table 2. The tests were performed on 5 to 9

different days (exceptions: rat 44, one specimen; rat 106, 4 specimens), at periods varying from 4½ to 8 months after operation. In addition to the unquestionable albuminuria of the obese rats, casts were found in profusion and red blood cells were present.

TABLE 2

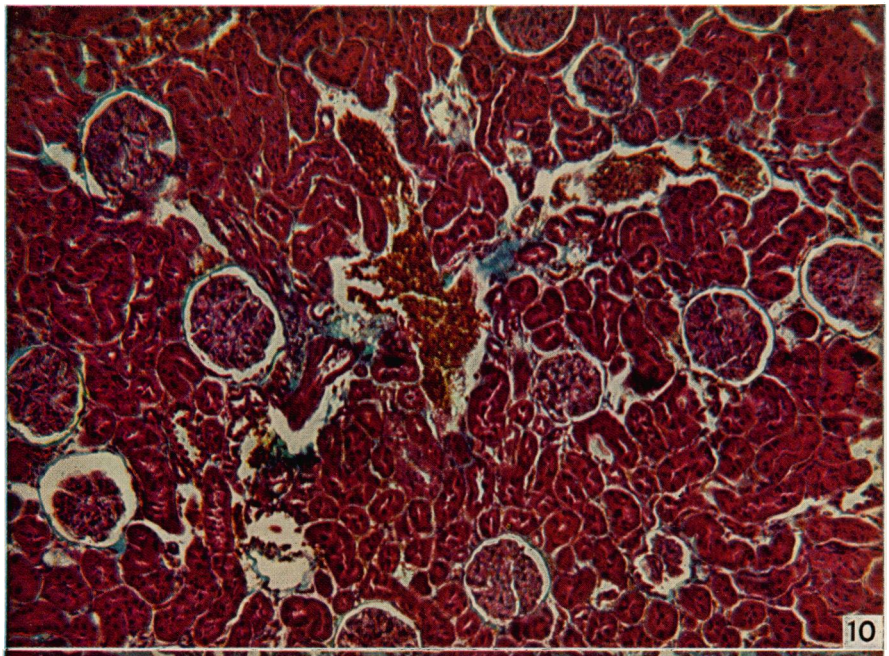
INCIDENCE OF ALBUMINURIA IN OBESE RATS AND CONTROLS*

Obese rats			*Controls*	
52	+ + + +	(Casts)	C 11	SPT
90	+ + + +	(Casts)	C 91	SPT
53	+ + +	(Casts)	C 12	SPT
69	+ +	(Casts)	C 68	SPT
71	+ +	(Casts)	C 72	O
94	+ +	(Casts)	C 95	SPT
54	+		C 13	O
44	+		C 5	O
75	+		C 74	O
106	+		C105	O
98	SPT†		C 99	SPT

* Mean number of observations per rat = 7.
† SPT = slightest perceptible trace.

Photomicrographs of sections from the kidneys of rat 34 and its control (Figs. 10 and 11) reveal in the fat rat extensive hyalinization of the glomeruli, with generalized increase in connective tissue and round cell infiltration. The tubules were dilated, their epithelium was thin, and they contained both formed casts and amorphous material which was probably precipitated protein. Similar changes were found in the kidneys of rat 53, and to a lesser extent in those of rats 54, 69, 71, and 75 (no others have been examined). The control rats showed no corresponding involvement.

Abnormalities of kidney function have previously been reported in rats fed diets having a high nucleic acid content (Newburgh and Johnston[44]), and in rats fed diets containing casein rather than liver (Saxton and Kimball[56]). The present series of experiments derives its interest largely from the high incidence of kidney dysfunction in obese human patients (Preble,[45] Dublin and Marks,[16] Evans[18]). With the study of pancreatic diabetes reported by Brobeck et al.,[7] these observations appear to be of some clinical significance, deserving more adequate investigation.



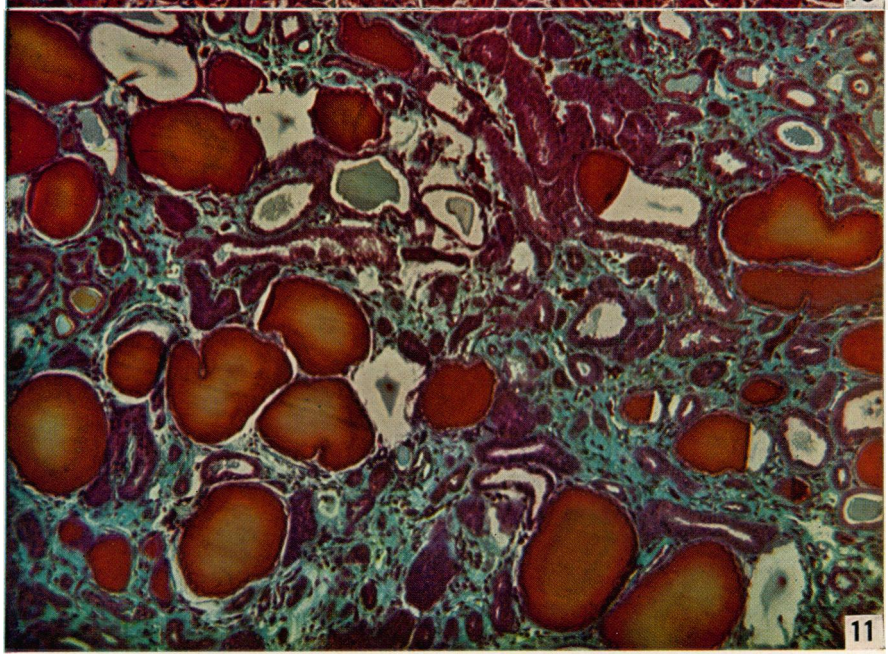


FIG. 10. Photomicrograph of a section from a kidney of control rat C4.
FIG. 11. Photomicrograph of a comparable section from a kidney of obese rat 34.

Autopsy data.

Gross examination of the carcasses and viscera of fat rats generally confirmed the work of Hetherington and Ranson.[27, 29] Many of the animals were almost incredibly obese, with an increased amount of fat in every depot of the body—beneath the skin, in the omentum, mesenteries, and retroperitoneal, perirenal, and pericardial tissues. Their gastro-intestinal tracts were found to be both dilated and hypertrophied, weighing (4 pairs of animals) approximately twice as much as those of control rats. This was undoubtedly a result of their hyperphagia, since a similar condition was present in trained normal animals which also ate relatively large amounts of food all at once (Tepperman et al.[61]).

TABLE 3

AUTOPSY DATA

Rat No.	*Post-operative day No.*	*Body weight gm.*	*Heart gm.*	*Liver gm.*	*Kidneys gm.*	*Adrenals mgm.*	*Ovaries mgm.*
34	444	796	2.05	17.40	5.91	....	46
52	320	426	1.10	13.60	3.25	....	....
53	318	418	1.30	12.00	2.51	44	23
54	318	650	1.60	18.10	2.80	52	32
69	236	569	1.15	18.00	2.60	51	21
71	236	564	1.40	14.55	2.55	64	30
75	236	527	1.10	18.40	2.20	52	35
90	402	598	1.60	25.50	3.53	89	23
94	216	436	1.00	10.00	1.75	49	35
98	216	400	1.15	9.70	2.00	37	25
104	163	464	1.15	14.70	2.20	50	49
106	177	568	1.00	15.30	2.00	60	30
Average		535	1.30	15.60	2.78	55	32
S. E.	±	33.4	0.094	1.250	0.322	4.47	2.56
C4		460	1.34	10.12	2.72	....	84
C11		253	1.20	8.80	1.65	53	85
C13		396	1.10	10.70	2.00	41	46
C72		300	0.90	10.00	2.00	50	108
C93		315	1.00	10.50	2.10	52	75
C95		250	0.80	5.50	1.45	41	49
C99		320	0.85	8.00	1.70	49	36
C105		344	1.00	6.70	1.80	56	58
C107		296	1.00	7.70	1.60	49	50
Average		326	1.02	8.67	1.89	49	66
S. E.	±	22.0	0.057	0.540	0.126	1.90	7.85

Statistical analysis (Table 3) of the weights of certain organs and endocrine glands showed that the hearts and kidneys of the fat animals were heavier than were those of controls, but the difference was not statistically significant. The ovaries, however, weighed significantly less in obese rats. Although Hetherington and Ranson[27] did not mention the latter change, they described testicular atrophy in the male rats of their series.

Livers of obese animals were almost twice the weight of those of the control rats. The percentage of ether-extractable lipoid in the former was slightly greater than normal when the animals were killed after a 24-hour fast, but when they were killed without previous fasting, the percentage of lipoid was significantly elevated to more than twice the normal level (Table 4). (It should be noted that in the normal rats the situation was reversed and the percentage

TABLE 4

BLOOD AND LIVER LIPIDS

Animal	*Total No.*	*State*	*Average*	*S. E.* ±	*Range*
		Blood fatty acids (m. eq.)			
Control	5	fasted	7.7	0.37	6.6–8.7
Obese	5	fasted	11.6	2.36	6.7–20.3
Control	5	fed	9.4	0.74	7.8–12.1
Obese	5	fed	17.9	1.77	14.6–24.4
		Blood cholesterol (mg. p.c.)			
Control	5	fasted	103	2.1	99–108
Obese	5	fasted	119	12.8	85–142
Control	5	fed	106	5.6	90–122
Obese	5	fed	156	9.7	122–176
		Total liver lipids (%)			
Control	3	fasted	9.08	0.331	8.50–9.55
Obese	3	fasted	12.06	1.536	9.73–14.95
Control	3	fed	7.90	0.576	7.17–9.04
Obese	5	fed	19.27	2.185	10.80–23.46

of liver lipoid was greater in the fasting than in the fed state.) Blood lipid levels of the obese rats varied in the same direction; when they were fasted before they were killed, blood cholesterol and fatty acid levels were higher than normal, but the elevation was without statistical significance. In the fed state the elevation from normal was more marked and proved to be statistically significant. Inter-

pretation of these data in terms of specific metabolic processes is not yet possible, but it seems reasonable to suppose that the abnormally high levels in fed obese animals reflected metabolic changes brought about by their unusual eating habits (Tepperman et al.[61]).

Hetherington and Weil[31] found that the weight gain of obese rats was due to storage of fat; true growth with protein synthesis is apparently not accelerated in hypothalamic obesity (Long[37]). Measurements of body length in this series showed no deviation from normal, although Hetherington and Ranson[30] previously reported that their rats with lesions were shorter than were control rats. This apparent discrepancy is probably attributable to Hetherington's having operated on immature, growing animals, while the present series included almost exclusively adult, "plateaued" females in which growth changes would be less likely to appear.

Hypothalamic lesions were fairly uniform from animal to animal, since similar coordinates were used for placing all lesions. Detailed analysis of variations has not been attempted. Lesions were usually placed 1 mm. from the midline on each side, and from 0.5 to 1 mm. above the base of the brain (as determined at operation by increased resistance to insertion of the electrode) at the level of the anterior border of the median eminence. A current of 2 milliamperes for 15 seconds usually produced a cone-shaped block of necrosis with the point of the cone near the fornix and the base of the cone at the base of the brain; this involved the ventromedial portion of the lateral hypothalamic area at that level and the ventrolateral portion of the central gray substance, including a corresponding portion of the ventromedial nucleus. This nucleus usually was not bilaterally destroyed. Photomicrographs were prepared from sections of the hypothalami of rats 69 and 71 to illustrate the type of lesion just described (Figs. 12 and 13).

Hetherington and Ranson[29] published rather complete descriptions of the hypothalamic lesions of the rats of their study. They were apparently able to interrupt, at various levels through the hypothalamus, paired systems which proceed caudally from their origin in the region of the ventromedial nuclei. Lesions of their animals differed from those of this series in that as a rule the latter were smaller and quite superficial. The neurons involved, or their processes, appeared to be located almost along the inferior surface of the brain-stem at this level. Hetherington (personal communication) has also noted this localization.

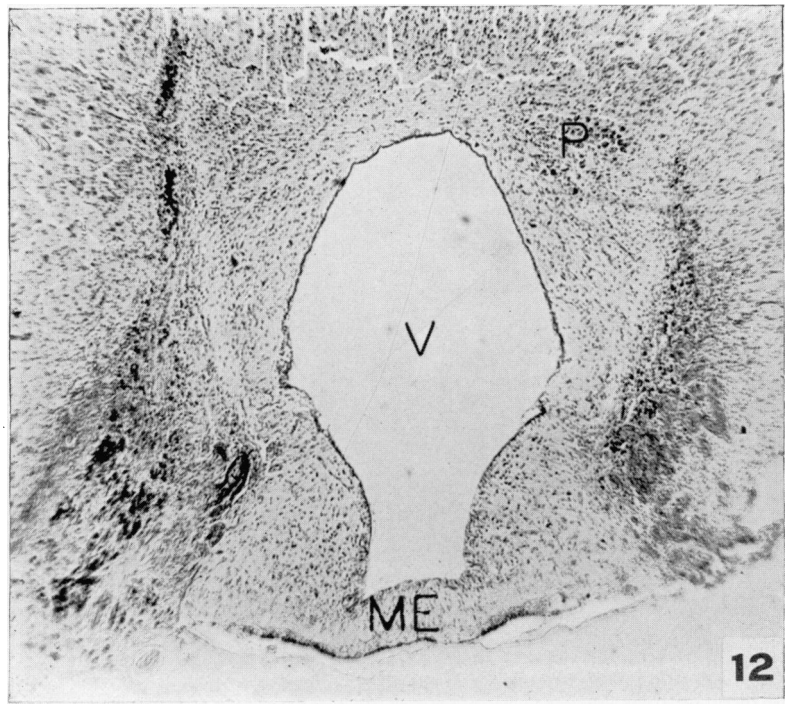
Discussion

Pathogenesis of hypothalamic obesity.

Hyperphagia has been previously described following experimental hypothalamic lesions. Keller, Hare, and D'Amour,[32] Keller and Noble,[33, 34] and Keller, Noble, and Hamilton[35] mentioned "enhanced appetite with adiposity" in dogs with hypothalamic lesions. Ranson, Fisher, and Ingram[46] observed "voracious" appetite in a fat monkey with pancreatic diabetes, but they were unwilling to attribute either the adiposity or the diabetes to the diencephalic damage. Following preliminary publication of the results of the experiments in this laboratory (Tepperman, Brobeck and Long[60]), hyperphagia and adiposity were described in rats with hypothalamic lesions (Brooks, personal communication), in monkeys with hypothalamic lesions (Brooks, Lambert, and Bard[8]), and in monkeys with lesions of the posteroventral region of the thalamus and the rostral mesencephalic tegmentum (Ruch, Blum, and Brobeck,[53] and Ruch, Patton, and Brobeck[54]).

The coexistence of hyperphagia and hypothalamic obesity is, therefore, well confirmed. Moreover, the following observations suggest that the adiposity is *caused* by the hyperphagia (rather than by some metabolic disturbance such as an inability to oxidize fat): (1) the rats appeared to be ravenously hungry immediately after operation; (2) when they were freely fed measured amounts of food there proved to be a significant correlation between the degree of hyperphagia and their excess weight gain (Fig. 1); (3) when they were fed *normal* amounts of food they ate quickly and greedily, consuming a 24-hour portion within a few minutes or a few hours; (4) when they were given opportunity to select the composition of their diet, they consistently neither chose nor rejected any particular component, while 2 of the 4 rats ate large amounts of olive oil; (5) during fasting (for as long as 27 days) they were able to use fat as a source of energy in amounts which closely approximated their previous caloric intake (see below). These observations lead almost inescapably to the conclusion that the animals suffered a disturbance which primarily involved the quantitative control of food intake.

This conclusion is supported also by the determinations of oxygen consumption and the paired feeding experiments. In 9 rats with



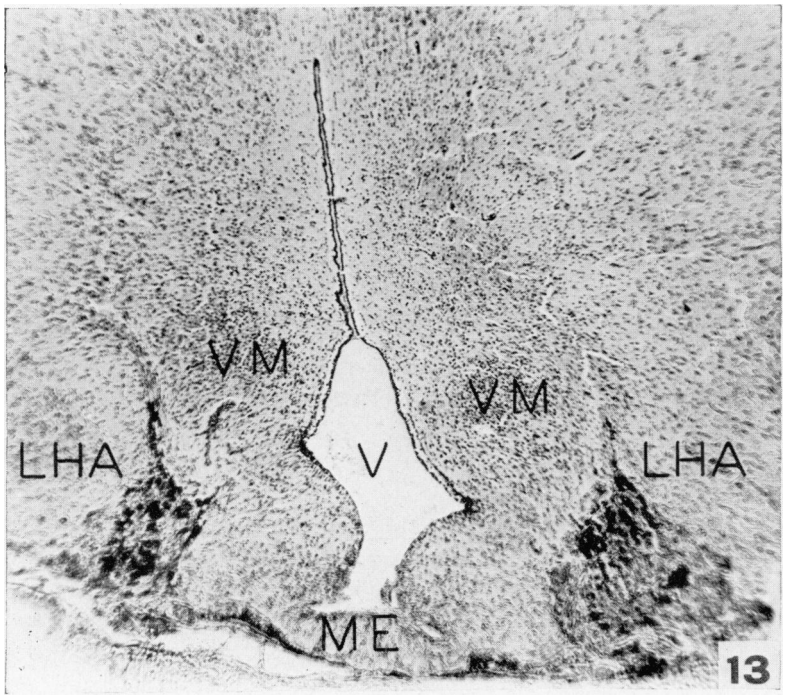


FIG. 12. Photomicrograph of hypothalamic lesions in rat 69. (ME—median eminence; P—paraventricular nucleus; V—third ventricle.)

FIG. 13. Photomicrograph of hypothalamic lesions of rat 71. (LHA—lateral hypothalamic area; ME—median eminence; V—third ventricle; VM—ventromedial nucleus.)

lesions, obesity developed on *ad libitum* feeding after the rate of weight gain had been found to be normal on paired feeding. Estimations of fasting oxygen consumption showed also that when body weights were comparable, oxygen utilization was the same in the operated as in the control rats, but as the animals became obese they used proportionately more oxygen (Fig. 6). A diminished fasting oxygen consumption, therefore, cannot be responsible for the progression of the adiposity. These observations confirm those of Means,[41] who noted a similar phenomenon in human patients. Strang and Evans[59] have pointed out, however, that the significance of observations of this kind frequently has been obscured by expressing oxygen consumption in terms of basal metabolic rate. To evaluate metabolism quantitatively, expression as actual oxygen consumption or with reference to the "ideal" weight of the patient is much to be preferred.

The importance of hyperphagia in the pathogenesis of hypothalamic obesity has been challenged by Hetherington and Ranson,[30] who proposed two alternate theories. In the first of these, they implied that the rats stored fat because they were unable to utilize it as a source of energy. This hypothesis requires a kind of deficit which does not appear to be present either in fat rats or in the fat monkeys of Brooks, Lambert, and Bard[8]; in both series of animals the fat of the adipose tissue disappeared during complete starvation. In the case of the rats, the fat was roughly accounted for on a caloric basis as follows: At the time of initiation of the fast, rat 104 and rat 106 (Fig. 4) were maintaining an almost constant obese weight on a daily intake of from 60 to 75 calories. During the fast they lost weight at a rate of about 8 grams per day, which is equivalent to 72 calories per day if the loss is assumed to have been due solely to oxidation of fat at 9 calories per gram. (Such an assumption is not wholly justified, for they must have been losing also a small amount of protein and some water. At the same time, their total oxygen consumption was probably proportionately decreased.) This rather exact correspondence seems to indicate, however, that oxidation of fat was supplying most of their energy. With the results of the other experiments enumerated above, these observations suggest, contrary to the opinion of Hetherington and Ranson,[30] that the adiposity does not cause, but rather follows, the increased appetite.

Hetherington and Ranson's second theory[30] was based on their observation that rats with lesions ran less than did normal controls when tested for activity in revolvable cages. They attributed adiposity to this relative inactivity rather than to the slight increases in food intake observed in the majority of their rats. Their data suggest that the experiment should be repeated, using rats in which the degree of obesity (and presumably also, hyperphagia) is more pronounced than it was in their series.

Increased food intake has been reported following experimental lesions of other parts of the central nervous system, but with the exception of the thalamo-tegmental lesions reported by Ruch, Patton, and Brobeck,[54] such hyperphagia has not been associated with obesity. The hyperphagia of animals with frontal lobe lesions does not cause excessive weight gain and apparently represents a compensatory adjustment of energy intake to the high level of expenditure associated with the motor hyperactivity which those animals suffer (Fulton, Jacobsen, and Kennard;[22] Richter and Hawkes;[49] Kennard, Spencer, and Fountain;[36] Ruch and Shenkin[55]).

Clinical literature contains a number of references to "morbid appetite" following central nervous system damage (see Fulton,[21] and Watts[62]). Although this increased desire for food has been ascribed to frontal lobe injury, the generalized nature of attendant neurological signs in the absence of adequate postmortem study suggests that hypothalamic dysfunction may have been present in cases of this type.

Hetherington and Ranson[27, 28] have effectively dismissed the previously widely held opinion that this type of obesity in human patients and in experimental animals depends in some way upon hypophysial disturbance. They proved that the adiposity could occur without direct hypophysial involvement, and eventually they produced the condition in completely hypophysectomized rats. The data of the present paper discredit also the supposition that the hypothalamus directly participates in the regulation of the biochemical processes concerned with fat metabolism. Hypothalamic lesions undoubtedly influence the metabolic processes of the animals, but such effects are evidently indirect, and are the result of hypothalamic hyperphagia (Tepperman et al.[61]). Metabolic changes present in animals with hypothalamic lesions have also been found in unoperated rats with abnormal eating habits evoked by training, and

certain of these alterations have been observed even in *in vitro* experiments (Dickerson et al.[14]).

Hypothalamic hyperphagia has been observed to cause obesity in the rat, the dog (Keller and others,[32, 33, 34, 35]) and the monkey (Brooks et al.[8]). In these three species, therefore, this type of obesity has been found to be not "endogenous" but "exogenous"—dependent upon the ingestion of more energy-yielding material than the body is able immediately to utilize.

Summary

Investigation of the energy metabolism of experimental hypothalamic obesity in adult albino rats has led to the conclusion that the greatest part of the chemical energy stored as excess fat represents extra food ingested by the animals. The rats appeared to be ravenously hungry almost immediately after operation, eating two or three times the normal amount of food daily when fed *ad libitum*. When they were fed normal quantities of food, they frequently ate a 24-hour portion within a few hours. A significant correlation was established between the extra food intake and excess weight gain.

Metabolic effects of the hypothalamic lesions appeared to be secondary to the hyperphagia. During self-selection feeding experiments and during complete fasting the animals were evidently able to use fat as a source of energy. Their fasting oxygen consumption was the same as that of control rats of comparable weight. On paired feeding, 9 animals with effective lesions gained weight at the same rate as their controls. In 3 other pair-fed rats, however, more rapid gains were observed and the suggestion is made that this phenomenon may have been related to the habitually rapid eating of the rats in question.

Albuminuria was observed in fat rats, with casts and red cells present in the urine. Chronic glomerulonephritis was found on microscopic examination of the kidneys of these animals. Additional changes discovered by postmortem examination included (besides the obesity): hypertrophy and dilatation of the gastro-intestinal tract, increase in size and weight of the liver, and a decrease in the weight of the ovaries of the obese rats. Blood and liver lipid levels were elevated in obese rats killed without previous fasting.

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