THE RELATION OF VARIOUS HYPOTHALAMIC LESIONS TO ADIPOSITY IN THE RAT

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ELEVEN FIGURES

Adiposity can be produced in rats by a simple operative procedure which involves the making of hypothalamic lesions with the Horsley-Clarke instrument (Hetherington and Ranson, '39, '40). The efficacy of the method has been confirmed by Tepperman, Brobeck and Long ('41).

Hetherington and Ranson ('40) described a series of twenty-one animals of various degrees of adiposity, with respect to growth, appearance, fat distribution, general physical condition, histology of the sex glands, and the correlation between the level of adiposity attained and the character of the hypothalamic lesion. At that time it was pointed out that the lesions found in all animals were unexpectedly large; and, in general, included much of the medial hypothalamus as well as some of the lateral hypothalamus on both sides from close behind the optic chiasma to a variable level in the mammillary body. Analysis of the differences between the lesions in various rats led to the opinion that some, at least, of this large area of destruction might be non-essential to the causation of the obesity.

The following report covers investigations which have verified this notion and offered some insight into the hypothalamic mechanism involved.

[1] Aided by a grant from the Committee on Research in Endocrinology of the National Research Council.

METHODS

The adaptation of the Horsley-Clarke stereotaxic instrument to rats was first described by Clark ('39), and, in particular, its application to the production of adiposity has already been explained in an earlier paper by the present authors ('40).

With the previous series of animals an effort was made to produce the maximum-sized lesion in the central hypothalamic region which could easily be made without killing the rat. Consistently successful results were obtained by inserting the electrode twice on both sides (at rostrocaudal intervals of 1 mm., and the same distance from the midline) and using a current of 2 milliamperes for 20 seconds at all four points of insertion. After larger lesions death usually ensued almost immediately; although, to be sure, an occasional animal has survived even greater damage.

In most of the present group the size of the lesion was as far as possible cut to approximately half that of the former. Instead of four insertions of the electrode, only two were made — one on each side of the hypothalamus. The same amount of current, 2 milliamperes for 20 seconds, was used at each point to be destroyed. In a few cases a single lesion in the midline, or two lesions (one rostral to the other) on the same side were made. As before, the electrode was lowered to the base of the brain and then raised 1 mm. before the electrolizing current was applied.

Lesions of this description were systematically distributed throughout the large region damaged in the previous (Rb 1–38) group of animals, from the immediate post-chiasmatic level through the mammillary body. Although the hypothalamic damage in these animals naturally displayed some variation in extent, all but a very few lesions were considerably smaller than those included in the first series.

Unlike the results of the earlier operations, also, the sequelae of the procedure just described were not particularly severe insofar as the acute postoperative stages were concerned. Animals commonly began eating on the same day the lesions

were made, or by the second day at the latest. Moreover, mortality was very low.

As usual, rats of a limited weight range have been used, in this case, from about 95 to 130 gm. at the time of operation. Evipal [2] (0.1 gm. per kilogram of body weight) was utilized for anesthesia. The standard procedure of measuring nose-anus and tail lengths of the rats at the times of operation and of sacrifice, as well as keeping weekly weight records was followed. The animals were kept in individual cages, in which food and water were present at all times. The diet fed consisted of bread and milk, grain, and canned dog food, supplemented by frequent additions of meat, carrots and other vegetables, alfalfa leaves, and Rockland rat food pellets.

When the animals were killed (by decapitation) the brains were removed and fixed in formalin, and the hypophyses in Champy's fluid. Cell (cresyl violet) and myelinated fiber (Weil) preparations of the hypothalami were studied histologically; while some of the pituitaries were serially sectioned at 3 μ and stained by the routine Severinghaus method.

RESULTS

Generally speaking, the data which have been accumulated from the present series of animals during the postoperative period of observation confirm and extend those reported for the original group (Hetherington and Ranson, '40). Some variations, however, have appeared.

As has already been mentioned, for example, the immediately postoperative stages are not so difficult for the animals to survive, and practically none die. Furthermore, it has turned out that animals with smaller hypothalamic lesions do not attain as high a level of adiposity as those with the larger lesions, nor is the onset of the obesity quite so rapid. In all probability, of course, these latter facts may be accounted for by the failure of the smaller lesions to destroy as many of the cells and fibers whose integrity is necessary for the normal processes of fat metabolism.

[2] Received through the courtesy of Dr. J. J. Kuhn of the Winthrop Chemical Co.

A minor feature of the general physical condition of the former series of animals was the frequency with which disorders of the skin and hair were to be seen. Roughness and yellowing of the hair, and scaliness and breaking of the skin were the chief troubles noted. The animals of the current series have not displayed such phenomena, except in a few instances, where the symptoms were not at all marked. Whether this healthier skin condition should be attributed to the lower degrees of obesity obtained in these animals, or to some other, uncontrolled factor is uncertain. It does seem likely that the obviously lower skin tension and the greater flexibility of the rats' bodies (enabling them to groom their coats more thoroughly) might be at least partly responsible for the difference.

Growth

In the earlier paper it was remarked that the obese males, which made up the major part of the series, almost invariably showed some degree of stunting in body length compared to their normal littermate controls. The few females of the series, on the other hand, did not display the same tendency, but the significance of the observation for the latter group was regarded with reserve.

The results obtained in the present series remove that doubt. Of the twenty-nine females, some fat and some not, reported here, only one (Rd-7, group C in the table) showed distinct evidence of dwarfing; in another (Re-16, group A) some stunting was suggested, but in the absence of any extensive data on normal variation in body length among the members of a single litter in our colony the observation is equivocal. Neither of these animals was at all obese. One of them (Rd-7) had been very sick for several weeks after operation and never seemed to overcome the lead its control gained during that time. In other words, a doubtful 7% (none obese) of all the females showed some dwarfing. The remainder definitely did not.

As for the fourteen males included in the present paper, the following, in brief, may be said. Some of them showed dwarfing and some did not. But of the fourteen only two, or possibly three (Rf-2, Rf-4, group B; Rf-5, group A) were fat; and of these three at least two, and probably all three were somewhat stunted. All of the males earlier reported were, of course, obese.

The significance of this observation, that obese females are not dwarfed, but obese males usually are, is not as yet understood. It would seem, naturally, to be a sexual difference; and might possibly be mediated through some hypothalamic influence over the gonads, perhaps via the hypophysis. Hypothalamic lesions do not, however, even when they cause marked obesity, always induce obvious aberrations of the reproductive glands. Clarification of the reasons for the phenomenon must await further study.

Sex cycles

The classical association of sexual dystrophy with adiposity in Fröhlich's syndrome has led most research work on the question into attempts to investigate both factors. The present example is no exception. Vaginal smears have been made on all of the females listed in the table except Rd-7 (group C) for at least 2 or 3 weeks just prior to sacrifice.

Inasmuch as results of the procedure have not been completely consistent, they should be treated conservatively. There has been an apparent tendency, nevertheless, for lesions in the rostral part of the hypothalamus (in the anterior hypothalamic area and in the rostral two-thirds of the ventromedial hypothalamic nucleus) to produce a condition of persistent vaginal estrus. The smears are characterized by the presence of great numbers of large nucleated epithelial cells, of cornified cells, of mixtures of the two, or of one and then the other alternately predominating — but in no case by a remission during which leukocytes appear in any numbers, or vaginal diestrus intervenes. Nine of the ten operated

females in group A showed such a picture. Re-17 alone ran normal, regular estrous cycles.

Animals with lesions in the middle part of the hypothalamus (in the caudal one-third of the ventromedial hypothalamic nucleus, and in the region of the premammillary nuclei) behaved quite differently. Eight of the ten operated females in group B ran rather characteristic estrous cycles, although two of these displayed cycles which were rather irregular in length. Of the remaining two females one exhibited persistent vaginal estrus, and the other very long phases of leukocytic infiltration and diestrus.

The animals with lesions in the caudal part of the hypothalamus (in the mammillary nuclei, and dorsolateral to them) afforded much the same results. Six of the eight operated females in group C on which data are available carried on normal or slightly irregular cycles. Two displayed persistent estrus.

The exceptional cases in these groups, while not numerous, damage what otherwise might be a good case for rostral hypothalamic regulation of ovarian cycles. But the seeming nonconformity of these females, except Re-17, may perhaps be explainable by the fact that an occasional animal in the normal colony (possibly 10% of the total) displays a state of spontaneous persistent vaginal estrus. It seems hardly likely, however, that the heavy majority of animals in group A showing continuous vaginal estrus could be accounted for in that way. One is rather more inclined to recall the findings of Dey, Fisher, Berry and Ranson ('40), who state that lesions in the anterior hypothalamus of female guinea pigs cause disturbances of reproductive functions.

It should be remembered that vaginal smears constituted the only effort to gauge the gonadal physiological processes of these rats. No attempt was made to determine whether they would mate, become pregnant, or bear young. What was sought was an indication of the condition of the sex glands; and what was found was that ovarian cycles were usually upset by lesions in the rostral hypothalamus, but usually pro-

ceeded normally, even in the presence of marked adiposity, after lesions placed in more caudal portions of the hypothalamus.

The latter finding is, for the present perhaps, even more interesting than the former, for it confirms the dissociation of adiposogenital dystrophy into two separate syndromes, a possibility suggested long ago by Camus and Roussy ('20).

Diabetes insipidus

Water consumption of all the Re-series of females was closely checked for a period of a week or so previous to termination of the experiment, but only four were discovered to display any appreciable polydipsia. Re-7 and Re-27 each drank about 35 to 50 cc. of water per day, an amount which could be classed as no more than mildly excessive. Re-16 drank from 65 to 115 cc. per day, a moderately high intake; and Re-36 drank 80 to 160 cc. per day, this being a rather pronounced polydipsia.

In the case of Re-7 (fig. 8) the lesion in the hypothalamus occupied the caudal third of the ventromedial hypothalamic nucleus, and the premammillary area on both sides, but did not involve the median eminence. At a level caudal to the attachment of the stalk, however, the lesion went to the base and evidently damaged the stalk, since this structure was noticed at autopsy to be unusually thick and tough (probably fibrous). The hypothalamus of Re-27 (fig. 5) contained a large lesion of the mammillary body. This lesion damaged the base of the brain caudally and the subjacent posterior lobe of the pituitary, the dural partition between them being exceptionally adherent to both.

The two more marked cases of diabetes insipidus showed no direct damage to the posterior lobe or stalk at autopsy, but it was noted that the neural lobe of both hypophyses was extraordinarily small and inconspicuous. Serial sections of the hypothalami revealed in both cases, besides some other damage, lesions which lay in the rostral portion of the hypo-

thalamus in the neighborhood of the optic chiasma. In Re-16 the apparently significant portion of the lesion lay against the dorsal and caudal aspect of the chiasma, on both sides, medial to the supraoptic nuclei. In Re-36 the seemingly relevant lesion extended from the base (around the midline) a short distance dorsally through the caudal edge of the chiasma. Both animals displayed much cell loss in the supraoptic nuclei and thinning plus increased cellularity in the median eminence. For the record, it should be stated also that both animals had bilateral lesions which damaged extensively (all the way to the base) the caudal reaches of the anterior hypothalamic areas, as well as the regions ventral to the fornices.

Adiposity

If adiposity were a process which develops to a constant level, its objective description would be a simple task. In the rat, however, no less than in the human, its course and outcome are exceedingly variable, and this fact introduces the experimental problem of measurement of degree of adiposity.

The most accurate method of expressing this factor would be that which was used by Hetherington and Weil ('40), who extracted all lipoids from the carcasses of their fat animals and expressed its quantity in terms of percentage of body weight. Such a technique applied to a long series of animals would naturally be enormously costly in terms of materials and time.

On the other hand, because it is wasteful of page space, the method used by the present authors in an earlier paper ('40) of publishing photographs and weight curves also has the drawback of being entirely inapplicable to a large group. Even worse, when the slighter grades of obesity are being dealt with, though significant, they are unimpressive to the inexperienced eye.

Consequently, a mathematical treatment of the data has been resorted to in this report. At first a simple ratio of body weight to body length was contemplated, but this has been

abandoned in favor of a practice advocated by Lee ('29), who was interested in the expression of metabolic results for white rats. Following Cowgill and Drabkin ('27), who applied the formula to the dog, Lee introduced a "nutritive correction factor" into his formula for determining the surface area of the rat. This "nutritive correction factor" consists of the ratio of the cube root of the body weight in grams to the body length (nose-anus) in centimeters, and indicates the nutritive state observed in the individual animal. Although these fat rats can hardly be said to be in a normal nutritive state, even so, it is felt that this ratio still expresses indirectly a significant relationship existing between the amount of fat laid down in an animal's body and the length of that body.

In the table summarizing autopsy data which follows, alongside each weight-length ratio is placed a symbol, either a minus-sign, or one, two, or three plus-signs, which represents a visual estimate of the degree of an animal's adiposity. This estimate was made at the time of sacrifice of the animal and was based on a careful inspection and comparison of the rat with its control. The animal was judged either not to be fat, or to be slightly, moderately, or markedly obese. These subjective impressions are not credited with the same value as the ratios extracted from the objective experimental results; but it is conceivable that constitutional differences may exist between different litters of even an inbred colony, and these differences might mislead an observer who took into account only absolute ratios when dealing with slight degrees of obesity.

As may be seen in the table, the two ratings of an animal in the two columns do not always give the same impression of its adiposity. Rat Re-20 (group A), for instance, was rated ++ in adiposity at autopsy, yet its ratio stood at only .300, a low figure. The same excess of enthusiasm is detectable in the estimate of Re-7 (group B) at +++, when its ratio was only .314. On the whole, however, the visual impression agrees fairly well with the calculated expression.

Table summarizing autopsy data on rats with various hypothalamic lesions.

TYPE OF LESION	RAT NO.	OP. CON	SEX	AGE	POST-OP. PERIOD	WEIGHT	NOSE-ANUS LENGTH	$W^{\frac{1}{3}}/L$	DEGREE OF ADIPOSITY	DEGREE OF DWARFING
				(d)	*(d)*	*(g)*	*(cm.)*			
A. Bilateral Anterior Tuberal Lesions	Re-13	O[1]	F	180	114	234	20.8	.296	—	—
	Re-14	O[2]	F	180	114	208	20.6	.287	—	—
	Re-15	C	F	180	—	228	21.0	.291		
	Re-16	O[2]	F	167	107	189	20.3	.283	—	?[5]
	Re-17	O[3]	F	167	107	348	22.2	.317	+++	—
	Re-18	C	F	167	—	225	21.5	.283		
	Re-19	O	F	192	130	323	21.4	.321	+++	—
	Re-20	O	F	192	130	261	21.3	.300	++	—
	Re-21	C	F	192	—	223	21.3	.284		
	Re-22	O	F	179	125	341	21.7	.322	+++	—
	Re-23	O	F	179	125	288	21.3	.310	++	—
	Re-24	C	F	179	—	253	21.8	.290		
	Re-35	O	F	141	99	277	20.2	.323	+++	—
	Re-36	O[2]	F	141	99	285	21.3	.309	+	—
	Re-37	C	F	141	—	200	20.9	.280		
	Rf-5	O[3]	M	136	80	347	20.5	.342	+++	++
	Rf-3	C	M	136	—	373	24.3	.296		
B. Bilateral Tubero-pre-mammillary Lesions	Re-1	O	F	173	109	279	21.5	.304	+	—
	Re-2	O	F	173	109	359	22.2	.320	+++	—
	Re-3	C	F	173	—	247	21.4	.293		
	Re-4	O	F	157	101	272	21.6	.300	+	—
	Re-5	O	F	157	101	316	21.6	.315	+++	—
	Re-6	C	F	157	—	224	21.5	.282		
	Re-7	O	F	144	100	333	22.1	.314	+++	—
	Re-8	O	F	144	100	319	22.3	.306	++	—
	Re-9	C	F	144	—	235	21.7	.284		
	Re-10	O	F	173	113	190	20.2	.284	—	—
	Re-11	O	F	173	113	205	20.5	.287	—	—
	Re-12	C	F	173	—	195	20.3	.285		
	Re-43	O[2, 4]	F	182	121	267	21.8	.295	—	—
	Re-44	O[2, 4]	F	182	121	205	21.2	.278	—	—
	Re-45	C	F	182	—	263	22.0	.291		
	Rf-2	O[2, 4]	M	133	77	380	23.8	.304	+	?
	Rf-4	O[4]	M	133	77	342	23.1	.303	?	+
	Rf-6	O[2]	M	136	80	325	23.1	.297	—	+
	Rf-1	C	M	133	—	385	24.7	.294		
C. Bilateral Mammillary Lesions	Re-25	O[2]	F	196	136	292	21.5	.308	+	—
	Re-26	O[3]	F	196	136	252	21.2	.298	?	—
	Re-27	O	F	196	136	207	21.1	.280	—	—
	Re-28	O	F	199	139	317	20.8	.327	+++	—
	Re-29	O[2, 4]	F	199	139	250	21.4	.294	—	—
	Re-30	C	F	199	—	241	21.6	.288		
	Re-31	O	F	214	148	303	20.7	.324	+++	—
	Re-32	O	F	214	148	261	21.0	.304	+	—
	Re-33	O[3]	F	214	148	292	20.9	.317	++	—
	Re-34	C	F	214	—	195	20.8	.279		
	Rd-7	O[4]	F	199	143	170	19.1	.290	—	+
	Rd-9	C	F	199	—	211	21.3	.279		
D. Midline Lesions	Rb-20	O[1]	M	167	99	285	22.6	.291	—	—
	Rb-21	O	M	167	99	285	22.4	.294	—	—
	Rb-22	O	M	167	99	287	22.8	.289	—	—
	Rb-24	C	M	167	—	302	23.1	.290		
	Rb-40	O	M	179	101	272	22.3	.290	—	+
	Rb-41	O	M	179	101	315	23.1	.294	—	+
	Rb-44	C	M	179	—	345	24.7	.284		
E. Unilateral Lesions	Rb-19	O	M	167	99	285	22.4	.293	—	—
	Rb-23	O[1]	M	167	99	248	21.9	.287	—	?
	Rb-24	C	M	167	—	302	23.1	.290		
	Rb-42	O	M	179	101	318	24.1	.283	—	—
	Rb-43	O	M	179	101	294	23.5	.283	—	?
	Rb-45	O	M	179	101	315	24.1	.282	—	—
	Rb-44	C	M	179	—	345	24.7	.284		

[1] Greater part of the lesion is in the dorsal hypothalamus.
[2] Lesion extends considerably beyond rostral boundary of zone.
[3] Lesion extends considerably beyond caudal boundary of zone.
[4] Lesion is rather markedly asymmetrical.
[5] ? indicates dwarfing (or adiposity as the case may be) doubtful.

No attempt has been made to divide these weight-length ratios arbitrarily into groups. Inspection of the table will reveal, however, that no female control exhibits a ratio above .293; the average of the ratios of all the normal females is .285. No female which was considered definitely obese during life, on the other hand, has a ratio below .300. Somewhere between about .295 and .300, therefore, lies the upper limit of the normal range for the females of this colony.

The mean of the ratios for the four normal males listed is .291; determined for a much longer series of normal males used in other experiments the figure is slightly higher — about .293 —, with an upper limit to the range of "normal" values at about .302.

In the table under discussion the animals are subdivided into groups according to the location of the lesions found in the hypothalamus. The classification is not particularly logical from the anatomical point of view, but is the only descriptively accurate one because of the regularity with which the Horsley-Clarke coördinates used approached each area. Of course the lesions differed somewhat from each other in detail. Some are more extensive, some more asymmetrical, some slightly more caudal or rostral than the others. Attention is called in the footnotes to a few of the more exceptional cases which are not to be analyzed at length later on.

The five groups may be described as follows:

A. Bilateral anterior tuberal lesions. In this section are found those animals having on both sides of the hypothalamus lesions which lie mostly in the rostral two-thirds to three-quarters of the ventromedial hypothalamic nucleus.

B. Bilateral tubero-premammillary lesions. Here are included the animals whose lesions lie for the most part in the caudal third of the ventromedial hypothalamic nucleus and the premammillary area.

C. Bilateral mammillary lesions. This group contains lesions confined mostly to the mammillary body or to the regions dorsal and lateral to it. Typical lesions in these first three zones tend to overlap each other because of their size.

D. Midline lesions. This group hardly requires further description; and it and the following one,

E. Unilateral lesions, include all such lesions at all levels in the hypothalamus.

As a glance at the table will show, none of the bilateral groups of lesions has a monopoly on the pronounced cases of adiposity. Neither is there any group which includes no negative examples. With the accumulation of more and more lesions, however, it has become apparent that adiposity is best produced by destruction lying in some one of a chain of positions from before caudalward; and that damage outside of this series of locations is consistently relatively ineffective. First to be described will be the lesions which did not cause any perceptible obesity.

The fornix may immediately be absolved of any responsibility for the production of obesity. It can be destroyed as in the case of Re-14 (group A; fig. 2) without provoking the onset of obesity; or it may be seemingly wholly intact as in the case of Re-20 (group A; fig. 1) where a large lesion occupying the caudal part of the anterior hypothalamic area and the rostral two-thirds of the ventromedial nucleus on both sides induced a very appreciable amount of fat deposition.

The same reasoning may be applied to the medial and lateral mammillary nuclei and the mammillo-thalamic tracts. In Re-17 (group A), for instance, where these structures are quite unharmed, adiposity is pronounced; but in Re-27 (group C; fig. 5) where they are almost completely destroyed, the result was negative.

Unproductive of obesity also have been lesions placed in the midline at various points from the chiasma to the mammillary body. Typical of these animals is Rb-21 (group D; fig. 4) in which a lesion beginning at the chiasma proceeds caudally to destroy the entire median eminence, and the adjacent arcuate nuclei on both sides to the level of the separation of the stalk and the tuber cinereum. At rostral levels the suprachiasmatic and ventromedial nuclei are both grazed. The data on diabetes insipidus have already been presented, but

it seems worth emphasizing at this point that there is no correlation between the occurrence of the two syndromes. Re-7 (group B) and Re-36 (group A) were both fat as well

ABBREVIATIONS

AHA, Anterior hypothalamic area
Arc, Arcuate nucleus
BP, Basis pedunculi
DM, Dorsomedial hypothalamic nucleus
DP, Dorsal premammillary nucleus
E, Entopeduncular nucleus
F, Fornix
Fil, Filiform nucleus
H, Medial habenular nucleus
HP, Habenulo-peduncular tract
IC, Internal capsule
LHA, Lateral hypothalamic area
LM, Lateral mammillary nucleus
ME, Median eminence
MFB, Medial forebrain bundle
ML, Medial lemniscus
MM, Medial mammillary nucleus
MT, Mammillo-thalamic tract
OC, Optic chiasma
OT, Optic tract
Ov, Suprachiasmatic nucleus
PC, Posterior commissure
PHA, Posterior hypothalamic area
PL, Prelateral mammillary nucleus
SC, Superior colliculus
SM, Stria medullaris
SMR, Submammillary recess
SO, Supraoptic nucleus
STh, Subthalamic nucleus
VM, Ventromedial hypothalamic nucleus
VP, Ventral premammillary nucleus
ZI, Zona incerta
III, Third ventricle

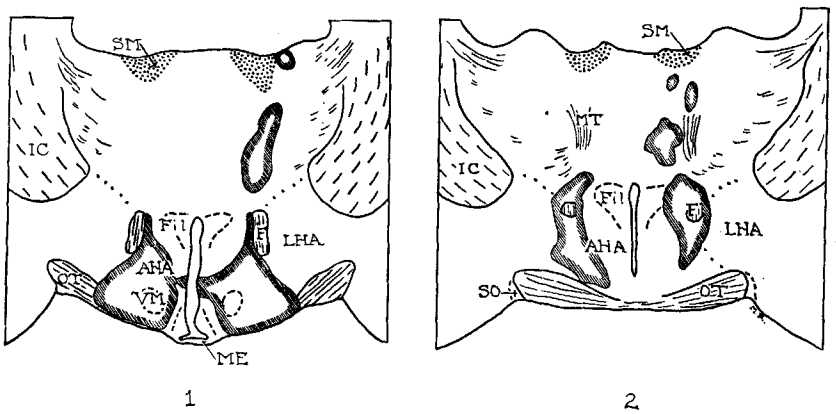

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Fig. 1 Transverse section through the hypothalamus of Rat Re-20 (mildly obese) at the level of the rostral poles of the ventromedial hypothalamic nuclei. The lesions in this and the following diagrams are bordered by a band of fine parallel lines. The boundaries of nuclei in the transverse sections are shown with heavy dashed lines.

Fig. 2 Transverse section through the hypothalamus of Rat Re-14 (non-obese) at the level of the caudal part of the anterior hypothalamic areas.

as diabetic; while Re-16 (group A) and Re-27 (group C) displayed polydipsia but were not obese.

Unilateral lesions, irrespective of size or rostrocaudal placement, have likewise failed to precipitate adiposity. The most striking example of these animals so far observed is non-obese Rb-45 (group E; fig. 3) which survived the infliction

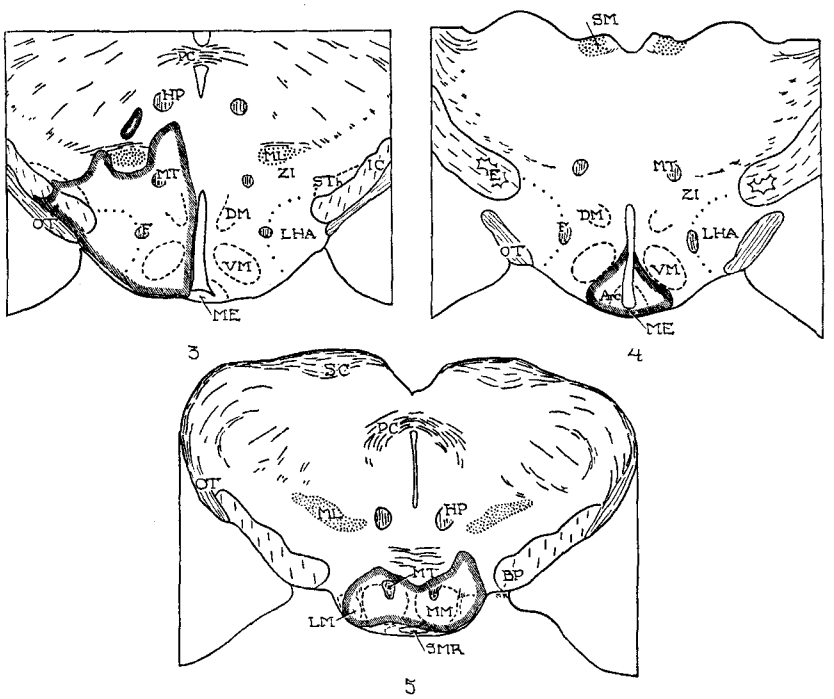


Fig. 3 Transverse section through the hypothalamus of Rat Rb-45 (non-obese) at the level of the middle third of the ventromedial hypothalamic nuclei.

Fig. 4 Transverse section through the hypothalamus of Rat Rb-21 (non-obese) at the level of the rostral third of the ventromedial hypothalamic nuclei.

Fig. 5 Transverse section through the hypothalamus of Rat Re-27 (non-obese) at the level of the mammillary nuclei.

of an enormous lesion extending from almost the anterior commissure rostrally into the mammillary body caudally. One side of the hypothalamus was almost entirely destroyed, from the base dorsally into the thalamus, and from the ventricle laterally into the internal capsule.

The results of damage to the anterior hypothalamic area are not so definite. Small lesions (Re-14, group A; fig. 2) and medium sized lesions (Re-16, group A) are ineffective, even if (as in the case of Re-16) they damage the rostral ends of the ventromedial nuclei. Rather more extensive damage of the caudal half of the area on each side, combined with destruction of about the rostral two-thirds of the ventromedial nuclei did, by contrast, produce some obesity in Re-20 (group A; fig. 1).

The positive side of the results so far obtained seems equally consistent. That is, adiposity is obtained if fairly symmetrical lesions are placed so as to destroy on both sides a good-sized portion of a large longitudinal zone in the hypothalamus. This zone begins rostrally at somewhere about the boundary between the anterior hypothalamic area and the ventromedial hypothalamic nucleus. Proceeding caudally it includes the ventromedial nucleus and perhaps the capsule of tissue immediately surrounding that nucleus, especially on its lateral and ventrolateral aspect. At the caudal end of the ventromedial nucleus the zone begins to swing away from the midline, and somewhat dorsally, probably expanding to some extent in cross-sectional area as well. It may or may not include the premammillary nuclei — or if it does may do so only incidently. At any rate, the responsive zone takes in more and more of the lateral hypothalamic area as it proceeds caudally, until at the level of the mammillary body it appears to be assuming a position lateral and dorsolateral to the mammillary nuclei. Beyond this region it has not been traced.

Lesions placed at three levels in this zone will be described as examples of the marked adiposity which can be produced by damage to the area. The first of these is Re-19 (group A). In figure 6 is shown a transverse section through the lesion at the level of its greatest size. This section is taken at about the middle of the ventromedial hypothamic nucleus. In figure 7 the lesion is drawn into a horizontal diagrammatic reconstruction of the rat hypothalamus seen from the dorsal side to show the rostrocaudal extent of the destruction. The

ventromedial hypothalamic nuclei are largely eliminated, except for a band of cells along the dorsomedial edge of the one on the right; and opposite them the regions ventral to the fornices, as well as the fornices themselves are involved. The caudal portions of the anterior hypothalamic areas are damaged, especially near the base, and the rostral half of the dorsomedial hypothalamic nucleus on the left side is destroyed.

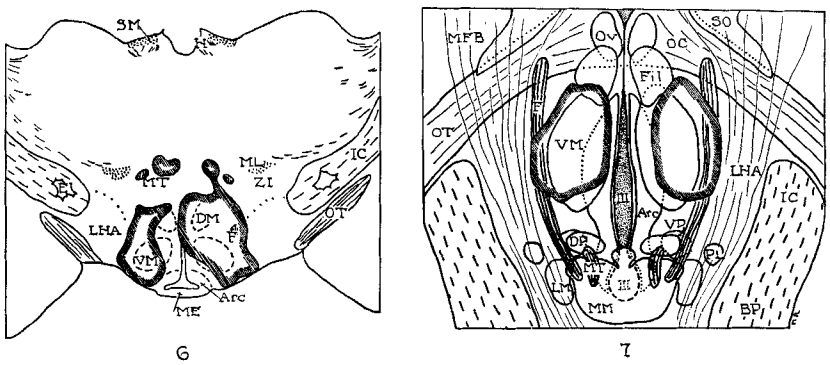
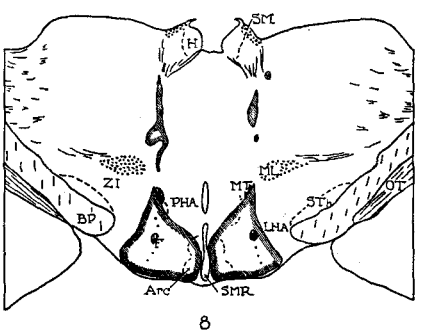


Fig. 6 Transverse section through the hypothalamus of Rat Re-19 (markedly obese) at the level of the middle third of the ventromedial hypothalamic nuclei.

Fig. 7 Diagram showing the rostrocaudal extent of the lesions in Rat Re-19. This and the following similar figures are copies of a diagrammatic reconstruction in the horizontal plane of the rat hypothalamus seen from the dorsal side. The most dorsal hypothalamic cell groups have not been represented. In the case of each animal the lesions have merely been superimposed upon the basic drawing.

Figure 8 is a drawing of a transverse section through the largest part of the lesion in Rat Re-7 (group B), which demonstrates the possibility of obtaining obesity by damage to a more caudal region than in the previous animal. The section is through the transitional zone between the ventromedial nucleus and the premammillary nuclei. The only cell groups which show up at this level, and they but poorly, are part of the periventricular group (p. arcuatus) and the posterior hypothalamic area. In Rat Re-7 the former and the ventrolateral parts of the latter are destroyed on both sides; but in addition (see fig. 9) the caudal thirds of the ventromedial nuclei and all of the premammillary nuclei are destroyed. The fornices are severed, the medial one-third to

one-half of the lateral hypothalamic area on both sides is injured, and the caudal half of the dorsomedial hypothalamic nucleus on the left is destroyed. The rostral edges of the medial and lateral mammillary nuclei on both sides are grazed.



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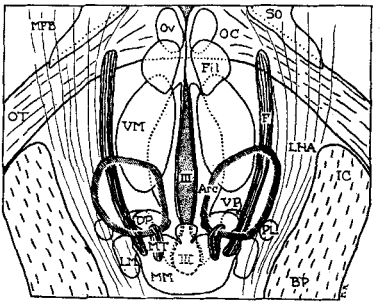

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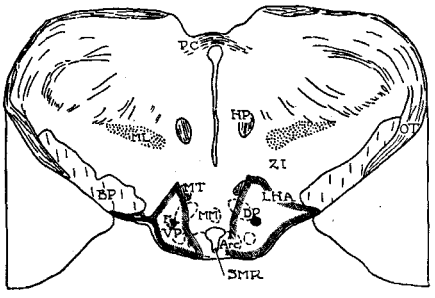
Fig. 8 Transverse section through the hypothalamus of Rat Re-7 (moderately obese) at the level of the transition zone between the ventromedial hypothalamic nuclei and the premammillary nuclei.

Fig. 9 Diagram showing the rostrocaudal extent of the lesions in Rat Re-7.



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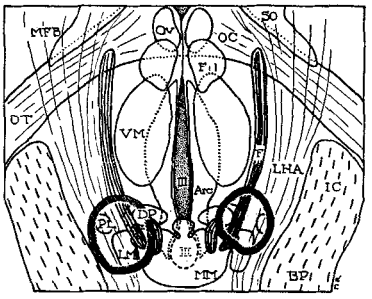

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Fig. 10 Transverse section through the hypothalamus of Rat Re-28 (markedly obese) at the level of the transition zone between the premammillary and mammillary nuclei.

Fig. 11 Diagram showing the rostrocaudal extent of the lesions in Rat Re-28.

The final animal to be considered, Re-28 (group C) is one which had the large lesions shown in figures 10 and 11. Figure 10 is a drawing of a section made through the greatest transverse diameter of the lesion, in the region between the premammillary and mammillary groups of nuclei. On both sides (fig. 11) the lesions destroy the ventral premammillary nuclei

and the lateral parts of the dorsal premammillary nuclei; all but the dorsolateral portions of the lateral hypothalamic areas are eliminated, and more caudally the lateral mammillary nuclei are severely damaged. Only small areas in the medial mammillary nuclei are involved.

Hypophysis

No comprehensive study of the cytological details in the hypophyses of the obese rats has as yet been attempted, nor have cell counts been made; but enough of the glands have been sectioned and stained for the submission of these brief preliminary statements:

While occasional minor damage is done to the dorsal surface of the pituitary, particularly the neural lobe, by lesions at the base of the caudal hypothalamus near the midline, in most of the cases of obesity reported here the hypophysis is definitely free of scarification. Connective tissue is present in the glands in normal amounts, no excessive vascularization is to be seen, and necrotic areas are lacking.

Furthermore, casual inspection of the glands has revealed no other conspicuous histological differences between these glands and those of the unoperated controls. In the absence of Golgi apparatus and mitochondrial studies, caution naturally should guide statements about the "normality" of the hypophyses of the animals, but at present it seems unlikely that serious morphological changes occur in the hypophysis of the rat as the result of hypothalamic obesity.

DISCUSSION

The present collection includes forty-three animals bearing a considerable variety of hypothalamic lesions. Although an exhaustive study of the effects of lesions throughout the entire hypothalamus is yet to be completed, this series indicates which structures are likely to prove most important in the control of fat metabolism.

It seems, in the first place, fairly clear that the mammillary nuclei, the fornices, and the mammillo-thalamic tracts are not

related in any important way to the regulation of fat metabolism in the rat, since their destruction does not cause obesity. These facts will probably appear a matter for no great surprise when one reflects that the mammillary nuclei and their associated fiber tracts are in reality more closely related to the newer portions of the rhinencephalon and to the cortex via the thalamus, than they are to those parts of the hypothalamus which undeniably are involved in the adiposity syndrome. This observation would hardly require emphasis were it not for certain findings by Bailey and Bremer ('21) and Grafe and Grünthal ('29), who claimed damage to the mammillary region in several obese dogs. Their results are probably explicable on the basis of coincidental damage either rostral or dorsal to the mammillary nuclei — a condition, incidentally, which the former workers recognized.

The situation with respect to the premammillary nuclei is very nearly, though not quite, as definite. Clearly, from the evidence which has been recited, to show that adiposity can exist in the presence of an unharmed structure is insufficient proof of the structure's inconsequence to the syndrome. Much more to the point is destruction of the structure itself with concurrent failure of the obesity to appear; and even this criterion might fall short under some conceivable faulty experimental conditions. In practice it has been impossible to destroy the premammillary nuclei by themselves. Their small size and intimate relation to neighboring hypothalamic areas almost preclude such a feat. There have accumulated some data from a small number of animals which indicate that when adiposity appears after destruction in this region, it is more probably because of damage done to the structures (possibly descending fiber conections) neighboring the premammilary nuclei. In the cases of Rats Re-10 (group B) and Re-26 (group C) — in which destruction of the nuclei was not quite complete — and Re-29 (group C) — in which destruction was complete — adiposity either did not exist, or existed only to a very slight degree. Other damage of course was present in these animals.

It must be conceded, nevertheless, that this picture is incomplete. Krieg ('32) and Gurdjian ('27) both observed the connections of the premammillary area with descending systems of fibers, which link the hypothalamus and more caudal portions of the central nervous system. It is not difficult to imagine that destruction of the premammillary nuclei or their fiber outflow might make the difference between appearance and non-appearance of adiposity when a limited amount of some other regions in the hypothalamus was simultaneously eliminated. According to this conception the premammillary nuclei might form a sort of coöperating, interacting complex with some of the other hypothalamic nuclei, the whole group, taken together, being in charge of fat metabolism.

More satisfactorily demonstrated than the foregoing effect is the negative result insofar as bringing on obesity is concerned of completely destroying the hypothalamus unilaterally. The explanation for this result is probably to be found in the influence over both sides of the visceral nervous system, and probably the somatic as well, which is exerted by either side of the hypothalamus. Karplus and Kreidl ('12) noted that bilateral command of the pupils and nictitating membranes of the cat was vested in each side of the hypothalamus; while Magoun, Ranson, and Hetherington ('38) and Harrison, Wang, and Berry ('39) found for several other autonomic functions that this spread of hypothalamic influence to both sides began even at levels in the brain stem rostral to the cervical cord.

This observation on adiposity merely highlights the ability of one side of the hypothalamus to carry on alone with considerable success the duties of both sides. Clark, Magoun, and Ranson ('39) found when they were studying temperature regulation in the cat that profound and long-lasting disturbances often were not secured in animals having decidedly asymmetrical lesions. And, indeed, this observation does not differ materially from our own ('40) findings that this sort of lesion did not produce a high degree of adiposity in rats.

In this connection, however, some reservation should perhaps be made. It would be of some theoretical interest, for example, if adiposity could be elicited in an animal by placing a lesion on one side of the hypothalamus in the region dorsolateral to the mammillary nuclei, as in Rat Re-28, and on the other side in the region of the ventromedial nucleus, as in Rat Re-19. Such damage would appear to be exceedingly asymmetrical, yet should at the same time be just as effective, if long descending pathways are in fact the means by which hypothalamic "centers" perform their duties in fat metabolism.

Finally, it appears unlikely that any direct connection between the hypothalamus and the hypophysis via the median eminence and hypophysial stalk is involved. The absence of conspicuous alterations in the pituitary, the failure of adiposity to follow destruction of the infundibulum, and the lack of correlation displayed in the development of adiposity and diabetes insipidus all argue against such a relationship.

That this should be so may seem strange to those who have attached considerable importance to the role of the hypophysis in pathological obesity. The foregoing should not be interpreted, however, so as to exclude the possibility that an "hypophysial adiposity" may exist as an entity separate from the "hypothalamic adiposity" under discussion. Nor is it even intended to convey the opinion that the hypophysis may not participate in some secondary way in the altered physiological state attending the body's augmented fat supply. This much seems certain, nevertheless: Direct innervation of the hypophysis from the hypothalamus via the stalk is unnecessary for the processes concerned in fat metabolism to proceed in an apparently normal fashion.

This discussion of ineffective lesions out of the way, the lesions which do result in adiposity may now be considered. In general, it may be said that there is an area, rather extensive in its rostrocaudal distribution, the bilateral destruction of which induces an abnormally great deposition of fat in the body. This zone, insofar as it has been worked out,

comprises the ventromedial hypothalamic nuclei and perhaps the tissue immediately rostral to and around them, and a contiguous but more vaguely outlined region caudal to these nuclei which extends back into the lateral hypothalamic area dorsolateral to the mammillary nuclei.

The boundaries of this zone have a certain indefiniteness which is commensurate with the difficulty of assigning distinct limits to most of the hypothalamic regions themselves. So far, however, there has been little to suggest that the caudal portions of the anterior hypothalamic area should be included in the effective zone, since even fair-sized lesions there fail to excite any measurable degree of obesity. When a large lesion in the caudal part of that area destroys a large rostral portion of the ventromedial hypothalamic nuclei some adiposity results, but even this may not be very impressive.

It should be emphasized, nevertheless, that larger lesions — lesions extensive enough to destroy the whole anterior hypothalamic area — should be tried before it is dismissed from consideration as a participating factor. Large lesions in the central part of the hypothalamus also, but especially those in the caudal and caudolateral parts of the hypothalamus would, after all, sever many connections coursing posteriorly from the anterior area. This point acquires particular interest in the light of the findings of Biggart and Alexander ('39), who noted some cases of adiposity in dogs after damage somewhat more rostrally placed than has been effective in the present series of rats.

Other areas which well deserve further attention are the lateral hypothalamic area (rostral to the mammillary region) and the posterior hypothalamic area. As regions through which pass many fibers descending from the hypothalamus they might well display some capacity for causing obesity when damaged. Still more instructive, however, might be lesions placed even more caudally than those reported here — lesions in the H field of Forel, and large lesions in the rostral part of the tegmentum.

For herein seems to reside the heart of the data so far accumulated: Lesions which occupy the medial hypothalamus, particularly the region of the ventromedial hypothalamic nucleus, or are placed in the caudal hypothalamus in a position to interrupt a large number of the descending fibers from the hypothalamic cell groups (Kabat, Magoun, and Ranson, '35) cause a marked degree of obesity. It should be possible, theoretically at least, to sever these descending fibers at a yet more caudal point in their course and obtain the same effect.

SUMMARY

Hypothalamic lesions have been placed in a series of forty-three male and female rats. In addition to observations on adiposity, data on growth, water consumption, and vaginal estrous cycles have been collected. The hypothalami have all been studied in serial section and some of the hypophyses of the obese animals have likewise been examined. The following is a general statement of the results.

Obesity is not produced in rats by lesions which destroy: (1) the fornix bilaterally with small damage to surrounding tissue in the anterior hypothalamus; (2) large portions of the caudal halves of the anterior hypothalamic areas symmetrically; (3) most of the mammillary body; (4) most of one side of the hypothalamus; (5) the midline structures in and close to the floor of the third ventricle, including the median eminence, and the arcuate and suprachiasmatic nuclei.

Obesity can be produced by fairly symmetrical lesions which destroy bilaterally: (1) most of the ventromedial hypothalamic nuclei together with some of the tissue immediately around them, especially on their lateral sides; (2) the caudal ends of the ventromedial hypothalamic nuclei, the premammillary area, and a considerable part of the lateral hypothalamic areas adjacent to it; (3) in the caudal typothalamus the areas which lie dorsolateral to the mammillary body. These pairs of lesions appear merely to represent interruptions at successive levels of paired systems (one on each side of the

hypothalamus, and each one capable of acting more or less independently).

The systems in question seem to arise rostrally in, or in the neighborhood of the ventromedial hypothalamic nucleus and to proceed caudally into the midbrain in the company of the medial forebrain bundle. The descending pathway may of course consist of chains of short neurons.

Ordinarily, adiposity in male rats is associated with some degree of stunting, in respect to body length, but the same is not true of females. It has also been found that adiposity caused by hypothalamic lesions lying caudal to the infundibulum is not usually accompanied by persistent vaginal estrus in the female. There likewise appears to be no significant correlation between the occurrence of adiposity and diabetes insipidus, the lesions which cause them being apparently fundamentally different.

The hypophyses of the obese rats which have been examined are in most cases quite clear of involvement in the destruction at the base of the brain.

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