THE SPONTANEOUS ACTIVITY AND FOOD INTAKE OF RATS WITH HYPOTHALAMIC LESIONS

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Bailey and Bremer (1921) speak of “apathy” in their two obese dogs which had hypothalamic lesions, and several of Brown’s (1923) fat dogs became “slug-gish.” Smith (1930), evidently referring to certain early postoperative symptoms, stated that rats which had received an injection of chromic acid into the hypophysis, presumably injuring the hypothalamus, like other rats with hypothalamic lesions, displayed periods of quiet interspersed with periods of excitement. Speaking also of rather early postoperative activity, Krieg (1938) mentioned, among other manifestations, an “emotionally hyperactive state,” and “depression.”

Although these and similar incidental references have been made by various workers to the behavior and activity of animals with damage to the tuber cinereum, apparently with but one exception (Richter, 1930) no one had tried until very recently to compare quantitatively the gross activity spontaneously exhibited by such animals with preoperative or normal values. Richter produced diabetes insipidus in seven rats by stabbing a short narrow blade through the sphenoid bone at a point he judged to be just rostral to the hypophysis. As yet the nature of these hypothalamic lesions, if indeed such they were, has not been described; but they probably occupied an area in the neighborhood of the median eminence. The result of this procedure was found to be essentially negative. Rats which had run well before the operation continued to do so afterward, and the poor runners remained inactive.

Food intake of these animals, Richter found, was likewise unchanged. Of course, none of the rats observed in these experiments became obese and it may be assumed that they did not bear the sort of hypothalamic lesions attributed by Hetherington and Ranson (1940) with the capacity to cause adiposity.

Other investigators, however, have reported a contrary finding. Keller, Hare and D’Amour (1933) and Keller and Noble (1935) observed enhanced food intake and a tendency to adiposity both in dogs with hypothalamic lesions and in dogs with a variety of pituitary injuries. Ranson, Fisher and Ingram (1938) noticed that one of their monkeys with hypothalamic lesions increased rapidly in weight and displayed marked polyphagia.

Finally in two simultaneous preliminary reports Tepperman, Brobeck and Long (1941) and Hetherington (1941) have added the most recent information on the subject. The former group found that certain rats with hypothalamic lesions became extremely obese and consumed approximately twice as much food

1 Aided by a grant from the Committee on Research in Endocrinology of the National Research Council.
as litter-mate controls. Hetherington, on the other hand, observed a group of operated rats which did not eat more than their controls, but which, nevertheless, in some instances did grow fat. The latter's animals were observed, in addition, to engage in a great deal less spontaneous running activity than did the controls.

The following experiments contain an elaboration of the results reported by Hetherington (1941) and a considerable amount of new material which has been added since that time.

**METHODS.** The present series numbers 18 male rats, 11 operated animals and 7 controls, run in groups of 6. Each group was made up of litter-mates. One control and one operated animal failed to survive the full length of time covered by the experiments and are not included in the results. Hypothalamic lesions were placed in the operated rats by the method described by Hetherington and Ranson (1940).²

For study of spontaneous running activity the type of cage, with slight modifications, described by Richter and Wang (1926) was used. The modifications were as follows: The living compartment is considerably smaller on these cages, being 3 inches wide by 5 inches high by 6 inches long. The revolving drum is a little larger, having a diameter of 15 inches. It is balanced in order to enable it to be stopped at any position, and revolves so easily that a weight of less than half a gram at the periphery will cause it to turn.

The cages were not kept in an air-conditioned room; consequently humidity undoubtedly varied over a considerable range. The temperature of the room, however, was kept within the range between 75° to 78°F. (Animals with hypothalamic lesions generally require a warmer room than normal for maintained good health.) They were subjected to 12 hours of illumination and 12 hours of darkness per day, the lights being controlled by a Tork electric clock.

The food supply was altered from group to group in the following manner: The first group received nothing but Rockland Rat Ration pellets for the first 5 weeks of the experiment. During the final 3 weeks the pellets were ground and moistened with water. The other two groups received a mixture made of 37 per cent ground Rockland rat pellets, 18 per cent ground dry white bread, and 45 per cent raw whole milk by weight. Needless to say, samples of this diet (as well as of the pellets first used) were dried daily to determine their moisture content; and all figures given in the results are dry weights calculated from the dried food residue collected at the end of each 24-hour period.

To determine the influence of activity upon food intake the second two groups were kept part of the time in small cubical living cages (7½ in. on a side), and the remainder of the time in the activity cages. The process was reversed with the other group, the first 5 weeks being spent in the ordinary living cages and the final 4 weeks in the activity cages.

**RESULTS.** The lesions found in the hypothalami of the operated rats need not be described in detail at this time. It is sufficient to say that they conformed

² For the Evipal anesthetic used in the operations we are indebted to Dr. J. J. Kuhn of the Winthrop Chemical Co.
in a general way with the lesions found in a former series (Hetherington and Ranson, 1940). As before, lesions producing the higher degrees of adiposity in this series lay on both sides in the region of the ventromedial hypothalamic nucleus and its immediate cellular environs. Lesions failing to precipitate the syndrome, or causing it to only a minor degree were rather markedly asymmetrical, not near enough to the base, or for some other reason inadequate.

When the experiment with each group of animals was terminated, the rats were weighed, anesthetized, and their body length (nose-anus) measured. They

**TABLE 1**

Table summarizing the data on age, weight, and body length of the rats at the time of the termination of the experiment

<table>
<thead>
<tr>
<th>RAT NO.</th>
<th>OP. OR CON.</th>
<th>AGE</th>
<th>WEIGHT</th>
<th>NOSE-ANUS LENGTH</th>
<th>W(^1/L)</th>
<th>DEGREE OF ADIPOSITY</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>days</td>
<td>grams</td>
<td>cm.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rf-1</td>
<td>C</td>
<td>133</td>
<td>385</td>
<td>24.7</td>
<td>0.294</td>
<td>+</td>
</tr>
<tr>
<td>Rf-2</td>
<td>O</td>
<td>133</td>
<td>380</td>
<td>23.8</td>
<td>0.304</td>
<td>+</td>
</tr>
<tr>
<td>Rf-3</td>
<td>C</td>
<td>136</td>
<td>373</td>
<td>24.3</td>
<td>0.306</td>
<td>++</td>
</tr>
<tr>
<td>Rf-4</td>
<td>O</td>
<td>133</td>
<td>342</td>
<td>23.1</td>
<td>0.303</td>
<td>+++</td>
</tr>
<tr>
<td>Rf-5</td>
<td>O</td>
<td>136</td>
<td>347</td>
<td>20.5</td>
<td>0.342</td>
<td>++</td>
</tr>
<tr>
<td>Rf-6</td>
<td>O</td>
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<td>325</td>
<td>23.1</td>
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<td>-</td>
</tr>
<tr>
<td>Rf-7</td>
<td>O</td>
<td>172</td>
<td>485</td>
<td>23.8</td>
<td>0.300</td>
<td>+++</td>
</tr>
<tr>
<td>Rf-8</td>
<td>C</td>
<td>172</td>
<td>413</td>
<td>25.1</td>
<td>0.297</td>
<td>+</td>
</tr>
<tr>
<td>Rf-9</td>
<td>C</td>
<td>157</td>
<td>371</td>
<td>23.9</td>
<td>0.300</td>
<td>+++</td>
</tr>
<tr>
<td>Rf-10</td>
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<td>157</td>
<td>473</td>
<td>24.3</td>
<td>0.321</td>
<td>++</td>
</tr>
<tr>
<td>Rf-11</td>
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<td>449</td>
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<td>0.327</td>
<td>+</td>
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<tr>
<td>Rf-12</td>
<td>C</td>
<td>died</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rf-13</td>
<td>O</td>
<td>153</td>
<td>413</td>
<td>22.9</td>
<td>0.325</td>
<td>+++</td>
</tr>
<tr>
<td>Rf-14</td>
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<td>died</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rf-15</td>
<td>C</td>
<td>153</td>
<td>323</td>
<td>23.1</td>
<td>0.297</td>
<td>+</td>
</tr>
<tr>
<td>Rf-16</td>
<td>C</td>
<td>153</td>
<td>335</td>
<td>25.0</td>
<td>0.302</td>
<td>?</td>
</tr>
<tr>
<td>Rf-17</td>
<td>O</td>
<td>153</td>
<td>349</td>
<td>23.5</td>
<td>0.299</td>
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<td>Rf-18</td>
<td>O</td>
<td>153</td>
<td>331</td>
<td>22.5</td>
<td>0.307</td>
<td>?</td>
</tr>
</tbody>
</table>

* Indicates presence of adiposity doubted.

were not always immediately killed. The data obtained at this time are summarized in the table, which shows age, weight, and body length, and several indices of degree of adiposity which will now be explained.

The formula \( W^{1/2}/L \), expressing the ratio of the cube root of the body weight in grams to the body length in centimeters, was borrowed from Lee (1929), who was interested in the expression of metabolic results for white rats. Following Cowgill and Drabkin (1927), who applied the formula to the dog, Lee used this "nutritive correction factor" to indicate the nutritive state observed in an individual animal.

In the table opposite the weight-length ratio of each operated rat 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 based on a careful inspection and comparison of the rat with its control, and signifies that the animal was judged either not to be fat, or to be slightly, moderately, or markedly obese. The two classifications of adiposity have not always given results completely consistent with each other, yet they do not in any case fundamentally disagree.

Figs. 1-4. Records of food intake and spontaneous activity (running) of obese and nonobese rats with hypothalamic lesions, and of their normal litter-mate controls. In figure 1 the change in diet at the end of the fifth postoperative week should be noticed. In figure 4 note the vertical scale for activity is different from that in the first 3 figures.

No attempt has been made to divide the weight-length ratios arbitrarily into groups. Inspection of the table will reveal, however, that no control rat exhibits a ratio above 0.302; the average of the ratios of the 6 normal males is 0.298. Determined for a much longer series of normal males used in other experiments the figure is slightly lower—about 0.293—with an upper limit to the range of normal values, as here, at about 0.302. No male which was considered definitely obese has a ratio below 0.304, and the fatter animals have ratios above 0.320.

All data secured from the activity cage experiments and from determinations of food intake are summarized graphically in figures 1 to 4.
The first 6 animals were placed in activity cages at the age of 6 weeks, and 4 of them were operated 2 weeks later. Two of the operated rats in a matter of 4 to 6 weeks showed an unmistakable degree of adiposity, while the other 2 retained an essentially normal appearance. In figure 1 the mean daily food consumption of each rat for any given week is averaged together with the mean daily food consumption of the other fat rat for the same week, and the average of the means is plotted on the graph as a single point. The same procedure is followed with the figures for daily activity, and is applied to the corresponding determinations for the pair of controls and the pair of nonobese operated animals. This has been done purely to reduce for the sake of simplicity and clarity the number of lines on the graph. With particular reference to the upper set of lines in figure 1 the point should be stressed at this time that the paired representation of food intake does not conceal an overlapping of the data of the normal and obese rats. Neither of the fat animals ate as large an amount of food as either of their control litter-mates.

As was mentioned before, the diet of these animals consisted during the first 5 postoperative weeks of whole Rockland rat pellets. On this diet the 2 nonobese rats maintained a considerably lower level of food intake than the others until the final 3 weeks of the experiment, when grinding and moistening of the food pellets (with water) seemed to exert a favorable influence upon their food consumption. The change apparently did not induce the 2 obese and 2 normal animals to alter their eating habits.

With regard to spontaneous running activity of the animals, the graph (fig. 1) speaks for itself. In this set of animals, and indeed in all the others as well (figs. 2–4), the trend is clear. Rats with large hypothalamic lesions in the region dealt with here evidently indulge in a great deal less running activity than do the majority of normal animals, or than they themselves did previous to the placing of the lesions. The change is striking and practically immediate, occurring within one or two days after the operation. There is a suggestion that the obese animals are even more inactive than those which do not grow fat (figs. 1, 4), but in view of the small number of animals tested, the difference might not be significant.

Figures 1 to 3 illustrate a state of hyperactivity which usually appears during the acute postoperative stage. Often rats with large lesions in this region of the hypothalamus will run almost continuously in an automatic, almost frenzied fashion for several hours after they awake from the anesthetic. This period may be succeeded by another lasting several days when the animals will seem to be stuporous, but will respond with exaggerated violence to slight tactile stimuli. The phenomenon was noticed many times in this laboratory, even long before the work on activity was begun. After the acute phases of the postoperative period are past the rats are rather lethargic, though this characteristic usually does not appear to partake of somnolence or a lack of alertness. They are, in fact, generally somewhat irritable and excitable for a number of weeks. With handling the rats after a time often lose this touchiness to a certain extent. (It should be mentioned, in passing, that more recently operated rats with lesions in the caudal hypothalamus have displayed neither the acute hyperactivity nor
the later hyperirritability of the rats just described. As a matter of fact, they tend to be rather amiable and more passive than normals. Even rats with the more rostrally located injuries will display the symptoms to a much slighter degree if the lesions in question are small.)

In a preceding section it was explained that the second and third groups of animals were fed a mixture of ground Rockland rat pellets, ground dry white bread, and raw whole milk. Food intake on this diet may now be considered.

Figure 2 shows how one operated rat which was accustomed to eating somewhat more than its control even before placing of the lesions, maintained, or even widened the margin between its food intake and that of its control after operation. After the animals were removed from the activity cages the food intake of the pair became more nearly equal.

In figures 3 and 4 is to be found a much clearer demonstration of the fact that these obese rats with hypothalamic lesions under certain circumstances will consume a good deal more food than do their litter-mate controls.

The final experiment, consisting of a comparison of the food intake of the animals during their sojourn in the activity cages, where it seems likely more exercise is taken by normal rats, with the food intake observed during the period spent in ordinary cages, has been rather inconclusive. In figure 2 there appears to be a slight decline in the food intake of both the normal and the obese rats after removal of the animals from activity cages. There furthermore seems to be a smaller difference between the intakes of the 2 rats, for which the more rapid descent of the curve for the fat animal is responsible. In figure 4 (where again the method of averaged daily means for the pair of controls and the pair of non-obese operated animals is used) is shown a small increase in food intake which occurred when the animals were placed in activity cages.

The rats represented in figure 3, however, reacted at first—apparently somewhat illogically—with a slightly increased food consumption after being transferred from their activity cages. Later these animals, too, decreased intake, and again the margin between the obese and the control rats narrowed because of the more rapid decline in intake by the fat rats. In any case, the changes in food intake which may be associated with the changes in spontaneous activity assumed here are not at all of the same order of magnitude as those which occurred in some of the obese rats, or even in the normal controls during the phase of rapid growth.

DISCUSSION. The phenomenon of adiposity is often regarded as a problem involving as causes either lack of exercise or over-eating, or a combination of the two. Doubtless in many cases these simple and easily understood factors may be an adequate explanation for excessive weight. In many other cases, however, as for instance in hypothyroid obesity, uncontrollable adiposity following pregnancy, and Cushing's syndrome, some more fundamental cause, intimately tied in with pathological physiology must be sought. (For critical analyses of recent theories regarding "exogenous" and "endogenous" obesity, see reviews by Wilder, 1938, and Bauer, 1941.)

Similarly, in the case of the experimental hypothalamic obesity being investi-
gated here, the most obvious explanations, decreased activity and augmented food consumption, were first taken up for examination, with the results that have been cited. It is true that these animals exercise a great deal less than normal rats. Yet animals which have somewhat similar lesions but which do not grow obese also indulge in much less spontaneous activity, though perhaps not as little as fat rats. It is also true that under certain circumstances, as when the food is softer, easier to eat, and possibly more palatable, the obese animals will consume excessively large amounts of it. This observation does not alter the fact, however, that these rats will also grow fat—though in all likelihood more slowly—even when food intake is limited to an amount equal to or even a little smaller than that of normal litter-mates.

When the simultaneous reports of preliminary work by Tepperman, Brobeck and Long (1941) and Hetherington (1941) appeared, the former group (who had done little or no work on activity) emphasized the high food intake of their animals; whereas the latter was more impressed by the tremendously decreased activity of the obese rats. Insistence upon the primary importance of either viewpoint would in all probability represent over-simplification of the problem, and this for at least two reasons.

In the first place, the two factors are complementary in their effect upon body weight. Both would tend to increase it. A very sedentary life, combined with a high caloric intake would seem to be an ideal combination for building up a thick panniculus adiposus.

Secondly, these two factors may be only symptomatic, and not fundamental. It is not difficult to imagine, for example, a condition of hidden cellular semi-starvation caused by a lack of easily utilizable energy-producing material, which would soon tend to force the body either to increase its general food intake, or to cut down its energy expenditure, or both. In this connection, it would be of great interest to determine whether these animals exhibit a preference for any particular class (chemically speaking) of foods.

It should be clearly realized that the apparent reluctance of the bodies of these fat rats to utilize their tremendous stores of fat is only relative and not absolute. Brobeck (1941) has stated that his fat rats can be fasted down to a normal body weight; and it has been noticed many times in this laboratory that a rat can stop eating and lose up to a third or more of its body weight before it recovers its appetite. These animals can, therefore, use fat as a source of energy if necessary, though perhaps at a low level of efficiency. The concept which comes to mind is one much like that expressed by Thomson (1938), who, discussing a somewhat similar matter, speculated upon the varying availability to the cell of different substrates of energy-furnishing material.

Evidence for a more basic disorganization of the physiological economy of these animals is not voluminous, but it is suggestive. To begin with, Hetherington and Weil (1940) showed that there was a pronounced deficit in the total body phosphorus of the obese rats with hypothalamic lesions. Although there was a co-existing calcium deficiency as well, the calcium-phosphorus ratio was irregularly altered in such a way that it was believed other phosphorus containing
materials besides bone had suffered. The importance of phosphorus in fat metabolism, particularly fat transport, and as a constituent of numerous physiologically important organic compounds in the body hardly requires elaboration.

In addition, Tepperman, Brobeck and Long found that the basal oxygen consumption of obese rats which had been either fasted for a long time, or pair-fed with their controls was low compared to the normals; while R.Q. determinations in the absorptive state were higher. Daily creatinine excretion was high in their rats, and carbohydrate metabolism in some instances appeared to be affected. Grafe and Grünthal (1929) found lowered B.M.R.'s in obese dogs which were supposed to have hypothalamic lesions.

It is argument along these lines which has suggested the imperative need for further fundamental physiological and biochemical research on rats displaying hypothalamic obesity. The ease with which the syndrome can be produced in the rat, and the wide variety of physiological techniques which can readily be applied to the animal make it an ideal subject for investigation.

SUMMARY

The spontaneous running activity both before and after operation of 10 rats with hypothalamic lesions frequently causing adiposity and of 6 normal litter-mate controls has been investigated. In addition the food intake of all the animals has been measured, in some cases both in activity cages and in ordinary cages.

It has been found that animals having bilateral lesions in the medial hypothalamus in the region in and around the ventromedial hypothalamic nucleus tend to indulge in much less spontaneous running than do the majority of normal controls, or than was exhibited preoperatively.

Food consumption of the obese operated animals may greatly exceed the intake of the normal litter-mate controls or may not exceed it at all, depending upon the nature of the food supplied. A soft palatable diet encourages maximum consumption, and a hard dry pellet diet apparently discourages high intake. Animals probably grow obese more rapidly on the former type of diet. The idea is suggested that the obese animal's efforts to increase food intake and cut down energy expenditure are indicative of a partial inability on the part of its physiological mechanism to metabolize easily all of its available food stores.

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