*J. Physiol.* (1963), **166**, *pp.* 395–407
*With* 1 *plate and* 4 *text-figures*
*Printed in Great Britain*



# HYPOTHALAMIC CONTROL OF ENERGY BALANCE AND THE REPRODUCTIVE CYCLE IN THE RAT

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(*Received* 5 *September* 1962)

Not all hypothalamic regulations can be identified with a separate nucleus or tract. This may reflect our failure to distinguish small structures regulating independent functions, or it may indicate more complex co-ordination. Some workers would divide the hypothalamus into a mosaic of more or less autonomous 'centres'; for example, the median eminence alone has been claimed to control independently virtually every pituitary secretion. This view is generally based on experiments in which disturbance of only one function has been studied at a time, but hypothalamic lesions, however small, seldom disturb one thing in isolation. The significance of the resultant syndromes depends on the regularity with which they can be reproduced and on the demonstration of a similar interdependence of functions in the intact animal.

Spontaneous locomotor activity is greatly increased during oestrus in the normal rat (Wang, 1923; Slonaker, 1925) and food intake is depressed (Slonaker, 1925). The inevitable result, as Brobeck, Wheatland & Strominger (1947) demonstrated, is a loss of body weight. The weight loss is made good during dioestrus, so that the rat oscillates about a state of energy balance rather than preserving it all the time. Here, then, is co-ordination in the intact animal of two aspects of energy balance with ovarian function.

All three components may be disturbed by hypothalamic lesions. Lesions in the ventromedial nuclei have been shown to increase food intake and to reduce spontaneous activity (Hetherington & Ranson, 1940; Brobeck, Tepperman & Long, 1943) although later workers have regarded the hyperphagia as the more predictable and important effect (Brobeck, 1946; Brooks, 1946). Lesions in the same position (Greer, 1953; Van Dyke, Simpson, Lepkovsky, Koneff & Brobeck, 1957) or rather further forwards (Hillarp, 1949) have been claimed to interfere with ovulation. Barraclough & Gorski (1961) and Gorski & Barraclough (1962) suggested that the ventromedial arcuate complex maintained a tonic discharge of luteinizing hormone in sufficient amount to cause oestrogen secretion but not

ovulation. Bruce & Kennedy (1951), however, found that lesions in this region often failed to disturb the oestrous rhythm, although they always prevented mating; the effect on mating was confirmed by Greer (1953). Kennedy (1955) suggested that the defect in mating was part of a general reduction in arousal. Our first object is to examine as many as possible of these variables together in a single series of rats with lesions.

If one mechanism could be shown to regulate both oestrus and the associated changes in energy balance, it might have a still wider function in the reproductive cycle, for there are similar but slower adjustments of energy equilibrium at puberty. Our second object is to examine the possibility that puberty and the restraint on appetite (Kennedy, 1957) and increased activity (Shirley, 1928) that accompany growth are causally related.

## METHODS

The rats were of the Lister hooded strain and were fed on M.R.C. diet 41B. All experiments were carried out in an air-conditioned room at between 75 and 80° F (24–27° C). The lights were turned on automatically at 6 a.m. and off at 6 p.m. The food hoppers were weighed daily and any spilled food was collected in plastic trays and also weighed. Vaginal smears were taken daily by washing the vagina with a few drops of saline from a pipette and examining the washings by phase-contrast microscopy while still wet. In tests of mating behaviour the female was introduced for several hours into a male rat's cage on the evenings of pro-oestrus and oestrus. Although the peak of oestrus, like the peak of running activity, occurs during the night (Levinson, Welsh & Abramowitz, 1941) this technique resulted in mating within the first hour with most normal females so long as the male's cage was used. A vaginal plug and the presence of sperm in the smear was taken as evidence of mating.

Bovine growth hormone in saline was injected intraperitoneally when appropriate in doses of 1 mg daily for 14 days. These experiments were controlled by preliminary injection of the same animals with isotonic saline for 14 days.

*Activity measurements.* The activity cages were modifications of those described by Richter & Wang (1926). Each had two parts, a living cage $8 \times 4 \times 4$ in. ($20 \times 10 \times 10$ cm), which allowed the rat to feed and lie down comfortably but gave no margin of space for running, and a revolving drum of wire mesh 1 m in circumference. The centre of the drum was mounted on one end of the spindle of an ordinary cycle hub, the shell which usually rotates being bolted to the framework of the cage. In this way the other end of the spindle was free as it rotated to close a microswitch operating an electric counter. The direction of rotation was immaterial, but a small weight attached to the rim of the drum ensured that it came to rest with the switch open. The opening between the two parts of the cage was only 5 cm in diameter, so that the rats were unable to get out of the exercise drum without first stopping it. These features are shown in Pl. 1, which also indicates another important point, that the cages were mounted side by side in pairs. Twelve such pairs were housed in one room and kept constantly occupied. The noise of the rotating drums and counters and the 'companionship' between the pairs acts as a considerable, although presumably constant, environmental stimulus. A further practical point is that rats must be introduced to the cages soon after weaning if they are to become fully active. The implication that running may be a learned activity will be examined later.

*Hypothalamic lesions.* The rats were anaesthetized with ether and the vault of the skull was exposed. The head was then fixed in a stereotaxic instrument, two holes were drilled with a dental burr just posterior to the bregma, and a unipolar platinum electrode, insulated

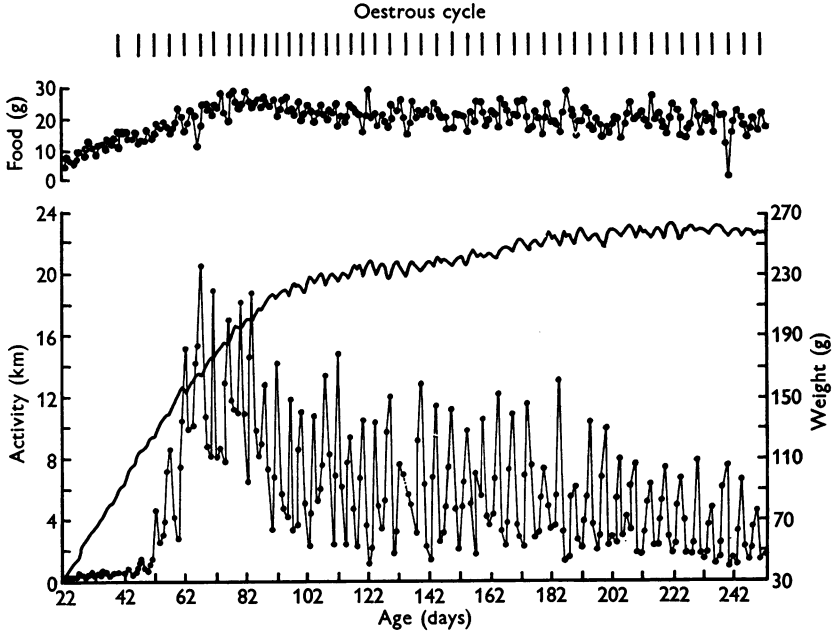
with glass except in its terminal 1 mm, was introduced into the brain. Bilateral lesions were placed 1 mm from the mid line, 1 mm above the base of the skull and 5·5 mm in front of the ear bars with a direct current of 2 mA for 10 sec. The wound was dusted with terramycin and sutured. No special post-operative precautions were taken.

*Histology.* The brains were fixed in Carnoy's fluid and other tissues in Susa. Paraffin sections were cut at 10 $\mu$ for brain and 5 $\mu$ for other tissues.

## RESULTS

### *Normal rats*

*The relation between oestrus and the energy cycle during development.* Text-figure 1 illustrates the events described above as seen in a typical normal female rat under the conditions of our laboratory. The animal was inactive before puberty and activity began just after cornified cells were first found in the vagina, building up with each successive oestrus to a

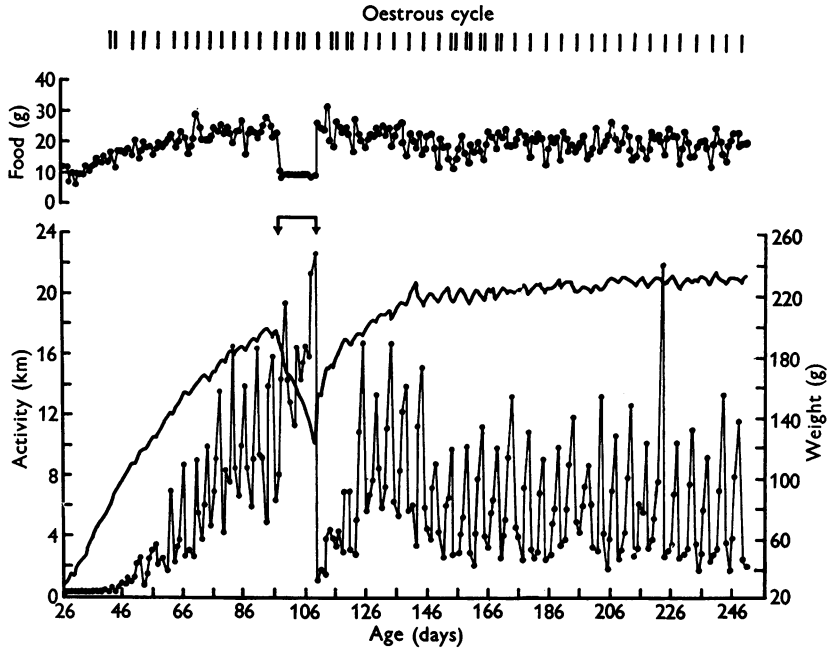



Text-fig. 1. Daily food intake, oestrous cycles, running activity and body weight of a normal female rat from weaning until 8 months old.

peak level. The age at which this peak occurred varied in the control series of 25 rats from 44 to 129 days and it was generally maintained for a few weeks before subsiding gradually over a period of 6 or more months to about half the peak level at 1 year old. Throughout adult life increased running and oestrus were synchronous and accompanied by reduced food intake and weight loss. Converse changes took place during dioestrus.

The changes in energy balance were not conspicuous during the early cycles after puberty, but became marked as growth slowed down.

*The effect of rapid growth on the relation between the cycles.* It is obviously impossible to say whether the gradual onset of activity is due to learning or whether full activity is delayed or inhibited by rapid growth. To attempt to clear up this point rapid growth was re-induced in rats in which it had slowed down. In the first experiment a group of 25 rats, each weighing about 200 g, was partially starved by giving only 9 g of food each day,



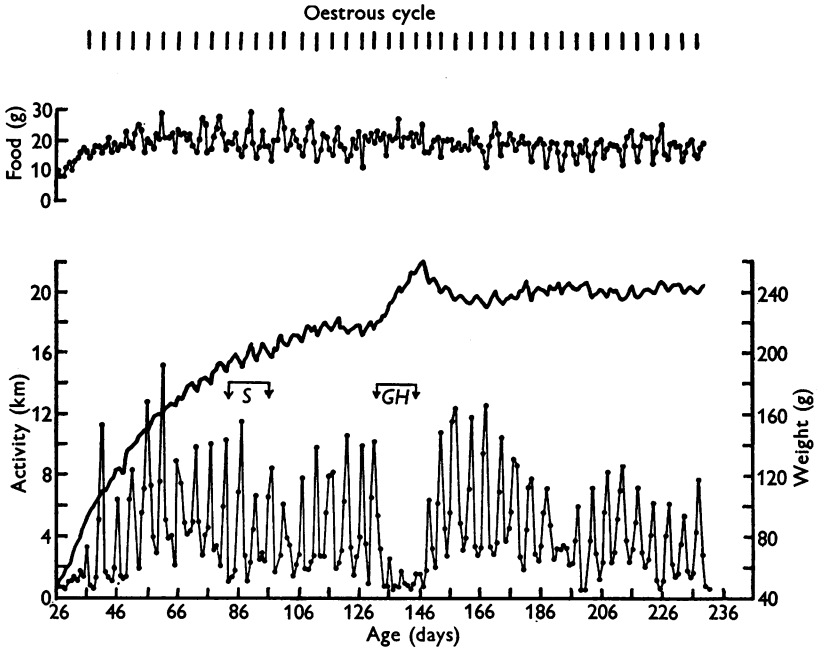

Text-fig. 2. Modification of the activity pattern by partial starvation and re-feeding. The inactivity of the rehabilitation period recapitulates that of the initial period of rapid growth.

until approximately 1/3 of the body weight was lost. The rats were then fed *ad lib.* again. Text-figure 2 illustrates the typical reaction. Activity increased during food restriction, particularly during dioestrus, but it was considerably reduced, virtually to the post-weaning level, at the beginning of re-feeding, only to increase again gradually as the pre-starvation weight was approached and growth slowed down again. In a minority of rats the oestrous cycle was interrupted by the under-feeding, and on re-feeding still further reduction of activity occurred.

Twelve rats were stimulated to rapid growth by injecting growth hormone. Text-figure 3 is typical of the results. As during the rehabilitation

in the previous experiment, rapid growth was accompanied by inhibition of running activity in spite of a normal oestrous rhythm.

*Post-weaning hyperphagia and inactivity.* In both the previous experiments the accelerated growth was accompanied by an increased food intake, but it is not possible to make a direct comparison with the post-weaning period because of the considerable difference in body size. At first sight the food intake appears to increase considerably from weaning




Text-fig. 3. Modification of the activity pattern by growth-hormone injection. Growth hormone inhibited running activity without affecting the oestrous cycle. Preliminary injections of saline were without effect. *GH* = growth hormone, *S* = saline.

to maturity (Text-figs. 1–3). Table 1 shows, however, that although the intake doubles in absolute terms during growth from 50 to 150 g, in terms of body weight it halves during the same period. The period of rapid growth and inactivity is therefore also a period of hyperphagia.

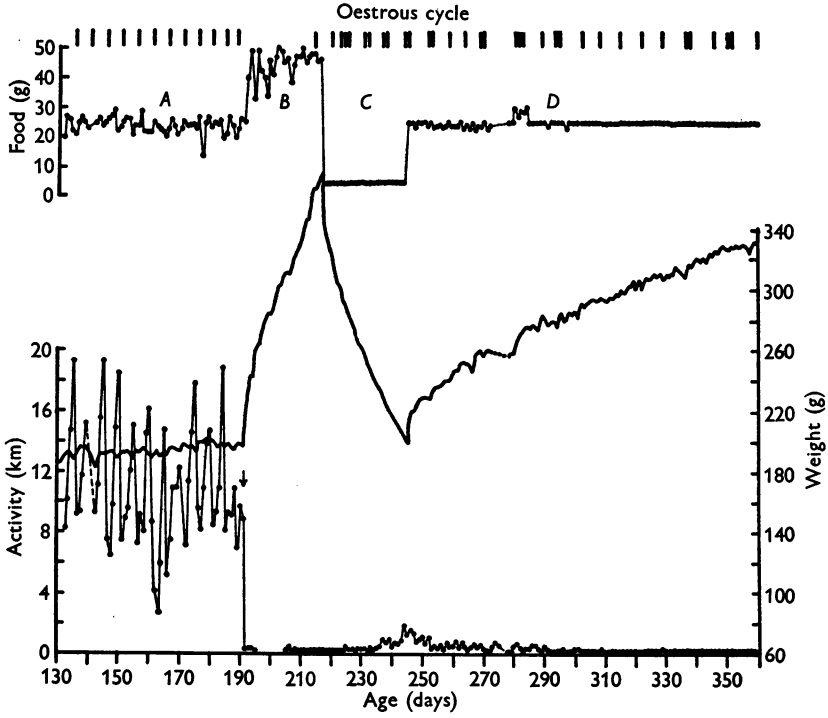
### *Operated rats*

*Hypothalamic hyperphagia and inactivity.* After hypothalamic operations had been carried out all the rats were allowed free access to food for at least 1 week and sometimes longer. Rats were regarded as hyperphagic which then ate between 30 and 50 g a day (normal in an activity

cage 20–25 g a day) and increased in weight by 3–9 g/day (normal 0·5 g/day). In a series of 25 operated rats 15 satisfied these criteria. All such animals were virtually completely inactive so long as hyperphagia continued. This can be seen in section *B* of Text-fig. 4. However, we have seen that even in normal rats rapid weight gain and hyperphagia induces inactivity, and in the present animals the mechanical effect of gross adiposity would be likely to restrict running still further. The food intake was therefore restricted to 10 g/day until the pre-operative weight was restored.

TABLE 1. The relation of food intake to growth

| Body weight (g) | Mean intake (g/day) | Intake (g/100 g) |
|---|---|---|
| 50 | 10·0 | 20·0 |
| 75 | 12·5 | 16·6 |
| 100 | 16·4 | 16·4 |
| 125 | 18·6 | 14·9 |
| 150 | 20·4 | 13·6 |




Text-fig. 4. The effect of hyperphagia (*B*) and subsequent underfeeding (*C*) on body weight, oestrous cycle and running activity of a young female rat. When the rat was later given the same daily intake of food (period *D*) as it had eaten before operation (period *A*) it gained weight, although less rapidly than in period *B*.

The effect of this food restriction on activity was found to depend on the severity of the initial hyperphagia. Severely hyperphagic animals (post-operative weight gain 7 g/day) behaved as shown in section *C* of Text-fig. 4; i.e. there was virtually no restoration of activity on reduction of weight. Less severely hyperphagic rats showed partial restoration of activity on reduction, usually to about half the pre-operative level, with abolition of activity again when they were subsequently re-fed.

Ten operated rats either failed to gain weight or gained more slowly than they should have done according to the criteria laid down above. They showed a transient post-operative inactivity but the activity either returned spontaneously within 2–3 weeks or could be restored to normal by restricting the food intake.

It has been questioned in the past whether the inactivity of rats with lesions is correlated with the severity of their obesity, and whether it in fact makes any appreciable contribution to the obesity (Brobeck, 1946). The severely hyperphagic rats were therefore given a daily allowance of food equal to their average daily voluntary intake before operation. The result is seen in section *D* of Text-fig. 4. In 60 days the rat gained 60 g in weight, compared with 20 g in the corresponding pre-operative period, and it continued to gain until it became grossly obese.

*Hypothalamic hyperphagia and the oestrous cycle.* The more severely hyperphagic rats from the activity cages were selected to study the effect of the obesity-producing lesion on the oestrous cycle. To these were added a larger group housed in ordinary laboratory cages, making in all 26 rats, which gained weight by at least 5 g/day. All were submitted to a period of food restriction as already described. The effect on the cycle will be considered in relation to the time after operation and treatment of the rats.

First, during the immediate post-operative hyperphagia all the rats showed a break of 12–15 days in their oestrous cycles, suggesting pseudo-pregnancy. This is a non-specific effect, which we have also observed in large numbers of rats with differently located lesions designed to cause diabetes insipidus, and after lesions which caused neither obesity nor polyuria.

Secondly, during food restriction half the rats showed constant vaginal cornification. This was in most cases a response to underfeeding, since most of the rats recovered normal cycles when re-fed. Moreover, we have observed the same response after underfeeding in intact rats.

Finally, the majority of the rats recovered a regular oestrous rhythm when they were given unrestricted food, although in some cases each oestrus lasted 2–3 days at first. The nearer the animal came to the fully established static phase of obesity, however, the less was the tendency to prolonged oestrus. The cycles during this phase are tabulated in the first

column of Table 2. A second and third column record the findings (not previously published) in a group of rats with obesity of rather less severity, and a non-obese group with lesions examined by Bruce & Kennedy in 1951. It is not intended to claim that the more severe the obesity the less the disturbance of the cycle, but merely that the technique we have used over a number of years to produce obesity has consistently caused no more and often less abnormality of the cycle than lesions which do not affect body weight.

TABLE 2. The effect of hypothalamic lesions on vaginal cycles

| | Lesions producing obesity | | |
|---|---|---|---|
| | Present series | Previous series | Other lesions |
| Number of rats | 26 | 22 | 23 |
| Normal cycles | 20 | 12 | 12 |
| Constant dioestrus | 3 | 8 | 5 |
| Constant oestrus | 3 | 0 | 3 |
| Irregular cycles | 0 | 2 | 3 |

TABLE 3. The effect of hypothalamic lesions on mating behaviour

| | Lesions producing obesity | | | |
|---|---|---|---|---|
| | Restricted food | Unlimited food | Other lesions | Normal controls |
| Number of rats | 16 | 18 | 20 | 26 |
| Normal pregnancies | — | — | 5 | 23 |
| No recorded mating | 16 | 18 | 8 | 1 |
| Mating without effect on cycle | — | — | 5 | — |
| Mating with prolonged break in cycle | — | — | 2 | 2 |

*Hypothalamic hyperphagia and mating.* Bruce & Kennedy (1951) tested the mating behaviour of their rats showing normal cycles after obesity was established, and although there is no reason to suspect that the adiposity affected the issue, we decided to meet possible criticism by testing ours while their weight was kept at the pre-operative level by food restriction. As mentioned earlier this reduced the number of animals showing normal cycles. Thirteen cyclic females and three with constant vaginal cornification were given the opportunity to mate on a total of 63 occasions, but never did. The latter animals were included because of the report by Austin & Bruce (1956) that such rats may show repeated matings. Table 3 compares this result with the earlier findings of Bruce & Kennedy, using only cyclic rats. In both cases lesions causing obesity were a complete block to mating, while more than half the non-obese rats with lesions mated.

*Localization of the lesions.* All the brains were serially sectioned. Detailed anatomical description of the lesions would be impracticable, but

in general those most effective in causing hyperphagia were symmetrically placed in the lateral part of the ventromedial nuclei. Those failing to cause obesity were usually further forward, although a few were posterior; none was in the lateral hypothalamus. Rats with lateral hypothalamic lesions are at least temporarily anorexic and lose weight, and such animals were deliberately excluded from the experiment on the basis of this behaviour. Three such rats which have been observed in activity cages were permanently inactive, even when they recovered from their anorexia, and further studies of the effect of such lesions are being carried out.

*Histology of the ovaries.* With the exception of the three rats with persistent vaginal cornification, all the ovaries were histologically normal, with abundant corpora lutea.

## DISCUSSION

Anand & Brobeck (1951) demonstrated beyond question that very small lesions (caused by 1 mA for 15 sec) invariably caused obesity when placed in or slightly lateral to the ventromedial nuclei of the hypothalamus. The lesions used here were a little larger, but the localization was the same. The present experiments confirm and extend Kennedy's (1961) finding that the greater the potential obesity following a hypothalamic lesion, the greater and more consistent is the interference with running activity. Moreover, they show clearly that the inactivity can be a cause and not merely an effect of the obesity, and is a direct result of the lesion. The ventromedial nucleus in the intact animal, therefore, can presumably both inhibit appetite and promote running. These changes no longer accompany oestrus in the operated rat, so it is probable that they are brought about during a normal oestrus by the ventromedial centre. Indeed, the fact that lesions in this region also invariably block mating during oestrus indicates that it may be the principal hypothalamic mechanism through which oestrogens influence behaviour. It was noted earlier that the peak of oestrus is synchronous with the peak of activity in the normal rat, and occurs at night.

The idea that the hypothalamus regulates mating behaviour, apart from ultimately controlling the release of ovarian hormones, was suggested by Ranson and his group. Fisher, Magoun & Ranson (1938) found that destruction of the anterior hypothalamus blocked mating in cats, and similar results were reported by Dey, Fisher, Berry & Ranson (1940) in guinea-pigs. Brookhart, Dey & Ranson (1940, 1941) showed that amounts of exogenous oestrogen which stimulated mating in castrate guinea-pigs failed to do so in animals with lesions. The rats with ventromedial nuclear lesions, which Greer (1953) found would not mate, exhibited constant

vaginal cornification. This condition may occur spontaneously (Everett, 1939), through pituitary operations (Pfeiffer, 1936) or after parabiosis with a castrate rat (Du Shane, Levine, Pfeiffer & Witschi, 1935); in all these cases it is a barrier to mating. Our rats with lesions in the ventromedial nuclei and normal ovarian cycles had abundant corpora lutea, indicating that they ovulated, and nevertheless they did not mate. This shows clearly that the region controlling behavioural oestrus is not entirely coextensive with that regulating gonadotrophin release.

The role of this part of the hypothalamus in motivated behaviour has received much attention recently (Miller, Bailey & Stevenson, 1950; Stellar, 1954; Morgane, 1961; Hoebel & Teitelbaum, 1962) and it is probable that the so-called satiety mechanism of the ventromedial nuclei and the closely associated feeding and drinking 'centres' in the lateral hypothalamus are intimately concerned in a variety of drives. All the details of this association are not yet clear, but to regard the ventromedial nucleus simply as a satiety centre reflects merely the preoccupation of individual experimenters.

There is at first sight a contradiction between our finding that the ventromedial region is not essential to the cyclic release of gonadotrophins and the demonstration by Barraclough & Gorski (1961) that stimulation of this site was pre-eminently successful in causing ovulation in the progesterone-primed, androgen-sterilized rat. However, their published results show that only about half the rats stimulated even in this position ovulated, and the proportion did not appear to vary much when stimulation was applied through most of the anterior and medial hypothalamus. The effect was simply the converse of what we found with lesions, and both findings contrast with the *consistent* inhibition of mating by lesions localized to the ventromedial area. The observation of Greer that such lesions may cause persistent vaginal cornification has been noted; other workers have had the same experience (Barnett & Mayer, 1954; Van Dyke *et al.* 1957), although this effect was first described with more anterior lesions (Hillarp, 1949). In our obese rats the effect was virtually never seen unless food intake was restricted, although we have observed it in normally fed rats with more anterior lesions. We shall show in subsequent papers that underfeeding also causes continuous vaginal cornification in intact rats.

These observations illustrate the difficulty of identifying discrete centres controlling single functions. Much of such localization is based on questionable premises. Gellert & Ganong (1960), for example, placed enormous lesions (caused by 10 mA for 10 sec) in the anterior hypothalamus of infant rats to accelerate puberty. Inevitably the sites of such huge lesions in these tiny brains overlapped in the mid line. It is doubtful whether such an area common to a number of larger lesions is a centre in

anything other than a geometrical sense. Our findings are more consistent with the idea of relatively extensive zones subserving individual functions but overlapping one another. The hypothalamic part of the gonadotrophin-releasing system can probably be limited to an area extending from the medial part of the ventromedial nucleus forward through the anterior hypothalamus, and having extensive connexions elsewhere in the limbic system (Harris, 1955; Elwers & Critchlow, 1960). Some further subdivision into an anterior part controlling ovulation and a posterior part controlling follicle development may be justified (Gorski & Barraclough, 1962) and the most posterior part we found to be particularly concerned with mating behaviour. Also, this posterior segment overlaps the region governing energy balance, which as Anand & Brobeck (1951) first showed extends laterally towards the medial forebrain bundle and forms part of an extensive 'motivational system' (Morgane, 1961).

With the exception of the dual role of the ventromedial nucleus, the two regions appear to operate independently, neither being affected by lesions of the other. The overlap of functions at the ventromedial nucleus has the interesting consequence that this centre can be stimulated either by a positive energy balance or by an increased oestrogen level, and both probably play a part in inducing the changes in feeding and activity at puberty. The inactivity before puberty was clearly related to the hyperphagia at the same time, and accords with earlier suggestions that the ventromedial nucleus is quiescent in the infant rat (Kennedy, 1957). The oestrous cycle in the adult was readily affected by changes in nutrition even after ventromedial lesions, and this raises the possibility of a nutritional stimulus to puberty. However, the reduction in food intake could not be the sole stimulus initiating the cycle if this involves, as Donovan & Van der Werff ten Bosch (1959) suggest, the removal of a hypothalamic restraint on ovulation, for, as we saw, hyperphagia does not cause any such restraint. Nevertheless, the synchronous onset of activity in the two hypothalamic regions suggests that some aspect of growth acts as a stimulus to both, and in the next paper we shall examine the possibility that the common factor depends on the change in energy balance around puberty.

SUMMARY

1. The 'spontaneous' running activity which accompanies oestrus in the female rat could be inhibited by rapid growth, either the natural growth which accompanies the first cycles after puberty, or growth induced artificially later.

2. It is likely that the inactivity in all these cases was due to high food intake.

3. Electrolytic lesions in the lateral part of the ventromedial nucleus of the hypothalamus increased food intake and consistently reduced activity; the inactivity in this case was shown to be a primary effect of the lesion and not secondary to the overfeeding.

4. The same lesions sometimes disturbed the oestrous cycle, but not more frequently than lesions which failed to cause obesity. Ventromedial lesions always prevented mating behaviour, however, even when they did not disturb the oestrous cycle.

5. It is concluded that the ventromedial nucleus in the intact rat can inhibit food intake and promote running, and that it produces these effects either in response to a positive energy balance or during oestrus under the effect of oestrogen. The nucleus also appears to play an essential part in mating behaviour, but not in the regulation of gonadotrophin release.

We are grateful to Miss P. Pledger for much help with the animal husbandry, and Mr K. Tingey for technical assistance. Professor F. G. Young made us a generous gift of bovine growth hormone and Mr D. Suttle helped greatly with the design and construction of the activity cages, and we should like to thank them both.

## REFERENCES

ANAND, B. K. & BROBECK, J. R. (1951). Hypothalamic control of food intake in rats and cats. *Yale J. Biol. Med.* **24**, 123–140.

AUSTIN, C. R. & BRUCE, H. M. (1956). Effect of continuous oestrogen administration on oestrus, ovulation and fertilization in rats and mice. *J. Endocrin.* **13**, 376–383.

BARNETT, R. J. & MAYER, J. (1954). Endocrine effects of hypothalamic lesions. *Anat. Rec.* **118**, 374–375.

BARRACLOUGH, C. A. & GORSKI, R. A. (1961). Evidence that the hypothalamus is responsible for androgen-induced sterility in the female rat. *Endocrinology*, **68**, 68–79.

BROBECK, J. R. (1946). Mechanism of the development of obesity in animals with hypothalamic lesions. *Physiol. Rev.* **26**, 541–558.

BROBECK, J. R., TEPPERMAN, J. & LONG, C. N. H. (1943). Experimental hypothalamic hyperphagia in the albino rat. *Yale J. Biol. Med.* **15**, 831–851.

BROBECK, J. R., WHEATLAND, M. & STROMINGER, J. L. (1947). Variations in regulation of energy exchange associated with estrus, diestrus and pseudopregnancy in rats. *Endocrinology*, **40**, 65–72.

BROOKHART, J. M., DEY, F. L. & RANSON, S. W. (1940). Failure of ovarian hormones to cause mating reactions in spayed guinea pigs with hypothalamic lesions. *Proc. Soc. exp. Biol., N.Y.*, **44**, 61–64.

BROOKHART, J. M., DEY, F. L. & RANSON, S. W. (1941). The abolition of mating behavior by hypothalamic lesions in guinea pigs. *Endocrinology*, **28**, 561–565.

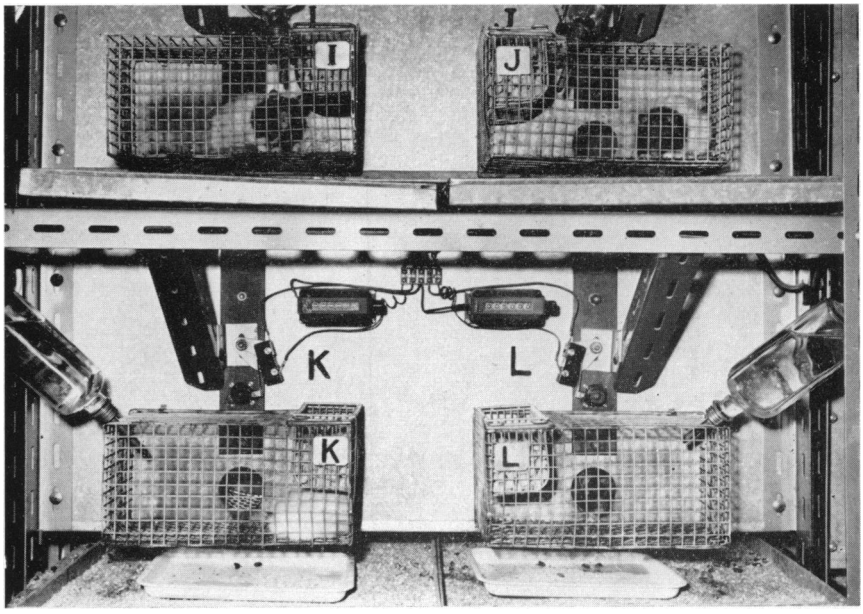
BROOKS, C. McC. (1946). Activity and the development of obesity. *Fed. Proc.* **5**, 12.

BRUCE, H. M. & KENNEDY, G. C. (1951). The effect of hypothalamic lesions on fertility and lactation in the rat. *Proc. Soc. Stud. Fertil.* **3**, 24–27.

DEY, F. L., FISHER, C., BERRY, C. M. & RANSON, S. W. (1940). Disturbances in reproductive functions caused by hypothalamic lesions in female guinea pigs. *Amer. J. Physiol.* **129**, 39–46.

DONOVAN, B. T. & VAN'DER WERFF TEN BOSCH, J. J. (1959). The hypothalamus and sexual maturation in the rat. *J. Physiol.* **147**, 78–92.

DU SHANE, G. P., LEVINE, W. T., PFEIFFER, C. A. & WITSCHI, E. (1935). Experimental 'constant estrus' and the notion of antigonadotropic hormones. *Proc. Soc. exp. Biol., N.Y.*, **33**, 339–345.

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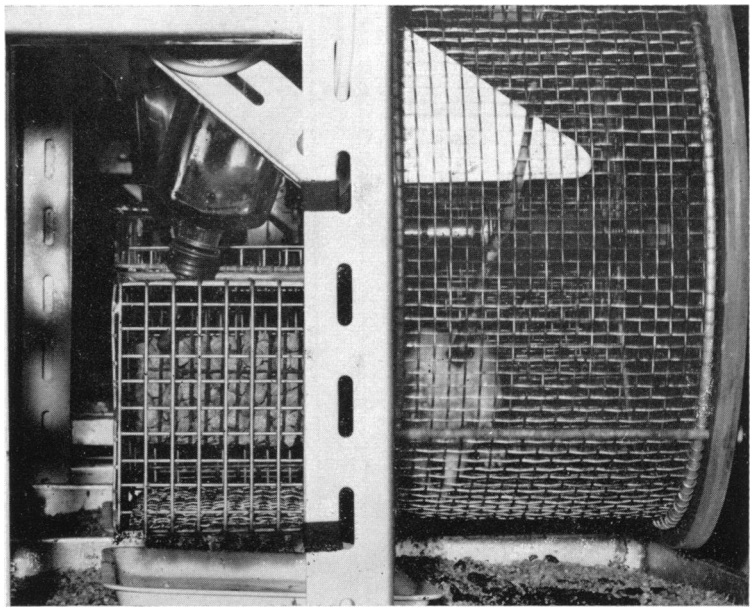

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ELWERS, M. & CRITCHLOW, V. (1960). Precocious ovarian stimulation following hypothalamic and amygdaloid lesions in rats. *Amer. J. Physiol.* **198**, 381–385.

EVERETT, J. W. (1939). Spontaneous persistent estrus in a strain of albino rat. *Endocrinology*, **25**, 123–127.

FISHER, C., MAGOUN, H. W. & RANSON, S. W. (1938). Dystocia in diabetes insipidus. *Amer. J. Obstet. Gynec.* **36**, 1–9.

GELLERT, R. J. & GANONG, W. (1960). Precocious puberty in rats with hypothalamic lesions. *Acta endocr., Copenhagen*, **33**, 569–576.

GORSKI, R. A. & BARRACLOUGH, C. A. (1962). Studies on hypothalamic regulation of F.S.H. secretion in the androgen sterilized female rat. *Proc. Soc. exp. Biol., N.Y.*, **110**, 298–300.

GREER, M. A. (1953). The effect of progesterone on persistent vaginal estrus produced by hypothalamic lesions in the rat. *Endocrinology*, **53**, 380–390.

HARRIS, G. W. (1955). *Neural Control of the Pituitary Gland.* London: Edward Arnold.

HETHERINGTON, A. W. & RANSON, S. W. (1940). Hypothalamic lesions and adiposity in the rat. *Anat. Rec.* **78**, 149–172.

HILLARP, N. A. (1949). Studies on the localisation of hypothalamic centres controlling the gonadotrophic function of the hypophysis. *Acta endocr., Copenhagen*, **2**, 11–23.

HOEBEL, B. G. & TEITELBAUM, P. (1962). Hypothalamic control of feeding and self stimulation. *Science*, **135**, 375–377.

KENNEDY, G. C. (1955). The central nervous control of food intake. *Advanc. Sci., Lond.*, 123–126.

KENNEDY, G. C. (1957). The development with age of hypothalamic restraint upon the appetite of the rat. *J. Endocrin.* **16**, 9–17.

KENNEDY, G. C. (1961). The central nervous regulation of calorie balance. *Proc. Nutr. Soc.* **20**, 58–64.

LEVINSON, L., WELSH, J. H. & ABRAMOWITZ, A. A. (1941). The effect of hypophysectomy on the diurnal rhythm of spontaneous activity in the rat. *Endocrinology*, **29**, 41–46.

MILLER, N. E., BAILEY, C. J. & STEVENSON, J. A. F. (1950). Decreased 'hunger' but increased food intake resulting from hypothalamic lesions. *Science*, **112**, 256–259.

MORGANE, P. J. (1961). Distinct feeding and hunger motivating systems in the lateral hypothalamus of the rat. *Science*, **133**, 887–888.

PFEIFFER, C. A. (1936). Sexual differences of the hypophyses and their determination by the gonads. *Amer. J. Anat.* **58**, 195–221.

RICHTER, C. P. & WANG, G. H. (1926). New apparatus for measuring the spontaneous motility of animals. *J. Lab. clin. Med.* **12**, 289–292.

SHIRLEY, M. (1928). Studies of activity. I. Consistency of the revolving drum method of measuring the activity of the rat. *J. comp. Psychol.* **8**, 23–38.

SLONAKER, J. R. (1925). The effect of copulation, pregnancy, pseudo-pregnancy and lactation on the voluntary activity and food consumption of the albino rat. *Amer. J. Physiol.* **71**, 362–394.

STELLAR, E. (1954). The physiology of motivation. *Psychol. Rev.* **61**, 5–20.

VAN DYKE, D. C., SIMPSON, M. E., LEPKOVSKY, S., KONEFF, A. A. & BROBECK, J. R. (1957). Hypothalamic control of pituitary function and corpus luteum formation in the rat. *Proc. Soc. exp. Biol., N.Y.*, **95**, 1–5.

WANG, G. H. (1923). The relation between 'spontaneous' activity and the oestrous cycle in the white rat. *Comparative Psychology Monographs* Vol. 2, Series 6. Baltimore: Williams and Wilkins.

## EXPLANATION OF PLATE

(*a*) Front view of activity cages, showing feeding compartments, switches and counters.

(*b*) Lateral view, showing rat running in drum carried on an extension to the spindle of a cycle hub. The triangular metal plate fixed immediately above the spindle prevents the rat from 'perching' there.