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The central nervous regulation of calorie balance

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Over short periods of a few days calorie balance does not appear to be regulated in any way we can analyse. A day-to-day record of the fluctuations in food intake and energy expenditure—the two components of calorie balance—usually yields a series of uncorrelated and apparently random numbers. It does not mean there is no relation between intake and output—there must be, or no long-term stability of body-weight would be possible—but it means that the relation is usually obscured by environmental variables. Under controlled conditions in the laboratory, one can detect regular rhythms of body-weight, appetite and activity in animals (Brobeck, Wheatland & Strominger, 1947), but they merely emphasize that calorie balance tends to 'hunt' or fluctuate around a mean value rather than to be rigidly preserved at all times. It is often suggested that, since eating is a periodic phenomenon rather than a continuous process, the study of energy balance should begin with the individual meal—that is with the mechanism of appetite and satiety. To do so, I believe, would be to risk missing the wood among the trees. We must start with the long-term behaviour of the animal. I say animal advisedly, because for obvious reasons central regulations are more easily studied in animals than in man, but I shall try to relate animal to human experiments as I go along.

Let me begin with two propositions which are common sense rather than physiology. First, I will repeat that there must be a long-term regulation of energy balance. Secondly, there is no *a priori* reason why this balance should be maintained by control of appetite alone, since it depends as much on calorie expenditure as on calorie intake. If you starve a laboratory rat for a few days and then restore its food, it will quickly recover its previous weight—one of the best possible proofs that energy balance is actively regulated. If you choose an elderly rat, it will put back the lost weight by overeating. But if the rat is a young one, it eats no more than it did before being starved—it reduces its energy expenditure and recovers its weight just as quickly (Adolph, 1947; Kennedy, 1950).

A great deal of nonsense has been talked about energy expenditure and body-weight, and the idea has been passed from physician to physician that one has to work like a lumberjack to lose a pound of fat. Even if one loses 1 lb, they say, one will develop an appetite that will put 2 lb back. But remember what Caesar said:

> Let me have men about me that are fat;
> Sleek-headed men and such as sleep o'nights.
> Yond Cassius has a lean and hungry look;
> He thinks too much: such men are dangerous.

Now it may have been Cassius's spareness that kept him active, or his restless drive that kept him lean. Both these effects can be demonstrated experimentally. In either event, Caesar knew better than many doctors. Exercise, of course, has a considerable energy cost (Orr & Leitch, 1938; McCance, 1953a,b; Passmore, 1956). Moreover, I am going to try to show that it is regulated through the same centres in the nervous system as is appetite. Incidentally, Caesar seems to have been right that motivation and emotional make-up were related to energy balance too.

Although we are not all as good at it as Cassius was, nearly all of us have some ability to control our body-weight automatically without thinking about it. The exception which proved this rule for me was a man of 21 who was referred to our clinic by Dr Leonard Simpson. He weighed 42 stones (588 lb) and had weighed 2 stones for each year of his age since he was about 14. Left to himself he ate about 7000 kcal a day. He was also inactive almost to the point of being bedridden, and although this inactivity had become more noticable as his obesity became grosser, he had never been a lover of exercise, even as a boy.

He was put on a 1000 kcal diet, and stuck to it quite docilely, with a minimum of supervision in hospital, for many months. Eventually he got down to 14 stones (196 lb). For a time he became more active, and even took up cycling. After leaving hospital he was not put on a fixed diet, but was taught to watch his weight and to adjust his intake accordingly. He has been reasonably successful in doing so for 4 years, although he has had a number of eating sprees which so resembled an alcoholic's binges that one psychiatrist labelled him a 'food addict'. His enthusiasm for pedal cycling soon waned, and he now rides an autocycle. His weight has risen again to 19 stones (252 lb).

Two things in this story remind one of experimental obesity in animals. First, the peculiar disorder of appetite—the astonishing hyperphagia when food was freely available, but the absence of resentment or apparent discomfort when food was short. Rats with hypothalamic lesions will eat two or three times the normal amount of their customary diet, but if getting food involves any effort or discomfort they eat less than normal rats (Miller, Bailey & Stevenson, 1950). So far as one can measure hunger drive in animals, it seems that they are not abnormally hungry, but there is something wrong with their stop mechanism which signals satiety. Now another feature of these rats is that they will refuse unattractive food, which normal rats are quite prepared to eat if nothing else is available. Adolph (1947) showed that rats normally eat for calories rather than for flavour. Puncturing the hypothalamus destroys this automatic 'calorimetric' regulation of appetite, and discriminative

attitudes to flavour and so on become relatively more important—the rat becomes something of a gourmet (Kennedy, 1950). Higher nervous centres are probably released from hypothalamic restraint. This has been called the 'encephalisation' of appetite by Anand, Dua & Chhina (1958). Hamburger (1960) has discussed this process in relation to human obesity in a recent review, and I need not say anything more about it here. Something of the sort seemed to have taken place in our patient, who had to be taught to restrain his appetite consciously, i.e. cortically, but unless his restraint was constantly reinforced he was liable to have an eating binge if he came across any food he particularly liked, just as a hypothalamic animal does.

The second similarity of our patient to an obese animal lay in his inactivity, and to judge from Mr Wardle's fat boy in *The Pickwick Papers*, this too has always been a familiar feature of human obesity. Let us look more closely at this aspect of experimental obesity.

Hypothalamic obesity—gluttony or sloth

Hetherington & Ranson (1940, 1942) first showed that lesions of the ventromedial nuclei of the laboratory rat caused obesity. They thought a reduction in physical activity was as important as overeating in causing the obesity. Later workers have been more impressed by the hyperphagia than by the inactivity, and have regarded this part of the hypothalamus simply as an 'appestat'. I believe this is an over-simplification.

In most studies, the obese rats have been housed in ordinary laboratory cages. Under these conditions even unoperated rats take very little exercise, partly because of the limitation of space, but even more because of a lack of what psychologists call environmental stimulus—in other words, the rats get bored. One can get over this problem by using the trick the schoolboy uses to liven up his white mice, one can give them a wheel to run around. In a cylindrical activity-cage of this type (Richter & Wang, 1926), with a circumference of about 1 m, a normal rat will run 10 miles or more in a day, which is the order of what one might expect under natural conditions. The cost of this exercise is met by an increase in food of about 60% over that of an inactive rat. Now some investigators have said that in spite of their reduced activity after hypothalamic operations, rats do not become fat unless they are overfed (Brooks, 1946; Brobeck, 1946). It is true in small cages, where, as I said, they expend so little energy even before operation that the reduction afterwards makes little difference to their energy balance. If a rat in an activity cage is given the same amount of food after operation as it ate before, however, it quickly gets fat (Kennedy & Mitra, unpublished findings).

It has also been claimed that there is no correlation between the reduction of activity after hypothalamic lesions and the degree of obesity. Confusion may have arisen here because inactivity can be an effect of obesity as well as a cause, and what one sees in a fat animal is a resultant of the two. Some years ago I made the records given in Table 1, which have not been previously published. Ten rats were submitted to hypothalamic operation. One showed only a transient postoperative inactivity and did not become fat. The next four became only moderately fat, but the

Table 1. *Relation between the obesity-inducing and activity-reducing effects of hypothalamic lesions in rats in cylindrical activity-cages*

Group	Rat no.	Weight increase in first 30 days (g)
1, transient postoperative reduction of activity. Full restoration spontaneously within 3 weeks, to more than 20 000 revolutions/day	1	12
2, permanent reduction of activity. Full restoration after starvation to more than 10 000 revolutions/day, with reduction again on feeding	2	56
3, permanent reduction of activity. Partial restoration by starvation to more than 2000 revolutions/day, with reduction again on feeding	3	50
	4	97
	5	63
4, permanent reduction of activity, unaffected by starvation (not reaching 2000 revolutions/day)	6	148
	7	112
	8	83
	9	141
	10	102

obesity was sufficient to keep them inactive; when they were starved to their original weight their activity returned to or towards normal. The rest of the rats were really obese, and they remained inactive even after starving. Mr J. Mitra and I have repeated this finding, and have collected more evidence of an intimate relation between the control of activity and of appetite, which will be published later.

Now let us go back for a moment to the failure of fat rats, and possibly of fat people, to work for food. Experimental psychologists have called this a reduction of hunger drive, the accent here being on hunger (Miller *et al.* 1950). However, in most of the tests of so-called drives, the rat has to do physical work to reach food, and this work is what is measured. Miss H. M. Bruce and I wondered whether it was the laziness rather than the hunger that was being measured in obese rats, and so we looked at another so-called drive—sex drive. We found that the majority of our operated rats had normal oestrus cycles, yet they would not mate (Bruce & Kennedy, 1951). Mayer (1957) has subsequently found the same in obese, hyperglycaemic mice. Now it is precisely at oestrus that running activity as measured in a treadmill cage is normally greatest, and therefore most obviously reduced by hypothalamic lesions. It seems likely, therefore, that any measure of motivated behaviour which involved a locomotor act on the part of the animal would show a reduction after hypothalamic puncture—the animals just can't be aroused. One may understand this better if one looks at the connexions of the hypothalamus with other parts of the nervous system.

Relation between the hypothalamus and other centres

The main associations are with the reticular activating system of the brain stem below and with the so-called limbic system or rhinencephalon above. It has been known for a long time that lesions in the brain stem tend to cause sleep or coma, and more recently it has been shown that stimulation of this part of the brain has the converse effect and causes the characteristic electrical discharges of arousal or wakefulness in the cortex. The functions of the limbic system are less clear, but it seems to

form a bridge between the phylogenetically ancient hypothalamus and reticular system and the newer centres in the cerebral cortex. One very credible theory is that the limbic system has reciprocal connexions with the other centres, through which the arousal stimuli from the reticular formation can oscillate back and forward for long periods—so-called reverberating circuits (Adey, 1957). However that may be, all three regions seem to act in concert to govern such things as sleep and consciousness, activity, emotion, the response to environmental stress and various endocrine functions. Which brings us back again to sleek-headed men, and such as sleep o'nights. Anyhow, right in the middle of this complex lie the ventromedial nuclei of the hypothalamus, and I think it needs little imagination to see in this the explanation of most of the clinical associations of obesity. To regard obesity simply as gluttony would seem to be as naïve neurophysiologically as it probably is biochemically.

Activity in man

A previous symposium of (The) Nutrition Society (1956) showed how difficult it is to measure a man's energy expenditure over any prolonged period. However, variations in locomotor activity in man can be measured with fair accuracy by a very simple device, the pedometer. It is a small instrument like a pocket watch with a system of balanced weights inside it. These respond to the up-and-down motion of walking, and the instrument can be calibrated to the average length of stride of any individual. It seems to have an accuracy of about $\pm 15\%$. Using it, Stunkard (1958, 1960) has made extensive investigations of locomotor activity in normal and obese subjects. He has found, as one might expect, that the general level of activity of man is greatly affected by psychological factors—it is greatly lowered, for example, during any form of depressive illness. Depression is common in obese patients, and may be a factor in the low activity they show as a group. Nevertheless, he has satisfied himself that there is the same sort of relation between activity and body-weight that there is in animals.

Johnson, Burke & Mayer (1956) also showed, in their surveys of obese children there, that the majority did not eat more but less than normal children. However, the number of hours in the week which they devoted to exercise was on the average one-third of the normal, and the exercise they did take was much less vigorous.

The mechanism of control

Finally, one may consider briefly how the brain might regulate energy balance. Earlier I quoted Adolph's (1947) conclusion that the rat ate for calories. Well, one might say, if it can measure its calorie intake, it can measure its calorie output, and balance the two. It is simply a matter of measuring the flow of energy through the body. It sounds so simple because of our habit as physiologists of calling all forms of energy by the same name—calories.

A great deal has been written about so-called 'central' theories of appetite—the best known are the thermostatic theory of Brobeck (1946) and the glucostatic theory of Mayer (1957). One says the brain reacts to the specific dynamic action of food—to

heat energy in fact—the other claims the stimulus is the rate of utilization of glucose —the dissipation of chemical energy. Both could explain eating for calories. But difficulty arises as soon as one tries to balance up energy losses. As I have indicated in Fig. 1, a great many calories leave the body neither as heat nor as chemical
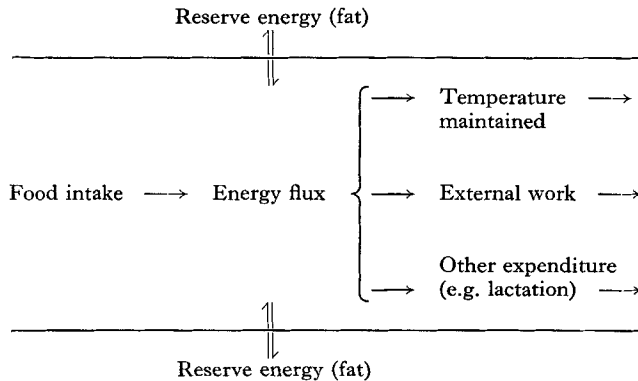

Fig. 1.   The diverse forms in which the 'energy' of food is utilized.

energy, but as mechanical energy used in external work. This energy later becomes heat, but only after it has left the body and the work is completed. Not only are different forms of energy involved, but they enter and leave the body in constantly varying proportions, and at different times. So measurement of the flow of energy through the body would require a series of different metering devices, one for each form of energy, and some sort of energy memory to put all the information together.

Fortunately, there is a much simpler solution, and I believe the key to it lies in the phrase 'energy memory'. The body keeps its own energy balance sheet automatically, i.e. biochemically, and there is only one form in which any significant amount of surplus energy can be stored—as fat. Fat provides the energy memory, and if fat stores are kept constant energy balance must be preserved. I believe that in the long term the hypothalamus modifies the general level of food intake and bodily activity in response to changes in body fat.

Moreover, this idea accords well with the observed effect of hypothalamic lesions. The only invariable index of the loss of hypothalamic function is the level of obesity which develops. A rat does not even have to overeat to get fat—as I showed it can do it by saving energy it previously wasted on running. Once the level of fatness is determined, it is actively maintained, and after starvation, for example, the same level of obesity is restored when food becomes available again. However, if the damage to the brain is increased by a second operation, a higher level of obesity will develop. When a steady state of obesity has been achieved, the food intake comes back to normal, just as it does in a fat patient. The only disturbance of appetite which ever does develop, in fact, is the transient increase incidental to getting fat. In all other ways, a rat with a hypothalamic lesion can regulate its appetite just as well as a normal rat. Both lesioned rats and normal rats make exactly the same quantitative adjustment of their food intake, for example, if the environmental temperature changes

(Kennedy, 1953). The hypothalamic disorder, in fact, is not primarily of appetite, it is of long-term energy balance.

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The effects of the endocrine system on calorie balance in man

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I don't know when the endocrine system was first saddled with the blame of obesity. The Chairman, who is an historian as well as a biochemist, may be able to tell us. When I was young, eminent physicians were often heard to speak of 'the pituitary' or 'the thyroid type' of obesity. Even today it is common for members of my profession to treat obesity with weird mixtures of tissue extracts containing those from the pituitary (which, remember, have no action when taken by mouth) and from the thyroid (which may or may not have some activity according as the patient has or has not a deficient secretion of thyroid hormone). I have, indeed a suspicion that thyroid hormone, in doses too small to affect calorie needs, may stimulate the appetite and increase the weight of the patient: the letter beginning 'Mrs So-and-So must have something wrong with her endocrine system. I have given her 2 g of thyroid a day, but her weight has increased even faster than before' seems to reach me with a frequency that might well be statistically significant.

I will therefore say that there is no good evidence that deficiency of any endocrine gland is an important cause of obesity. That deficient or excessive action may occasionally be a contributory factor is a possibility I propose now to discuss.

The posterior pituitary. This gland has undoubtedly a considerable influence on water balance and thus on body-weight, but its influence on calorie requirements is less well defined. Indeed all that is known is that in rabbits and rats the injection of