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Efficiency of Energy Utilization by the Zucker Hereditarily Obese Rat "Fatty"[1] (38569)

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An increase in efficiency of energy utilization by obese subjects is frequently alluded to in the literature of obesity, but has not been universally accepted. Evidence is cited by Bray and York (1) for rodents, by Sims *et al.* (2) for man, and there is a recent stimulating discussion of how this might come about, by Hegsted (3). The actual mechanism for the phenomenon remains unknown.

As further evidence that there can indeed be an increase in efficiency, a detailed study is here presented on the ability of the "fatty" to accumulate large fat deposits, given a normal or subnormal food allowance.

Experimental. This is a paired feeding experiment, with obese "fatties" paired in food intake to suitable lean controls. Six pairs of males started on experiment at 28 ± 3 days of age, were fed for 30 days, then analyzed for body composition (fat, water, nitrogen (4, 5)). Five pairs of females were carried on in the same way and terminated on the 74th day. The diet, L Sulfa, is a stock type diet based on skim milk, casein and wheat (for details of composition see (4)).

There were three special features in the experimental plan, all designed to make the "fatty" and its control more similar. (A) Controls as well as "fatties" ate two meals per day. They were allowed to eat *ad libitum* for an hour in the morning and again in the evening. Food cups were designed to minimize error from spillage and have been described elsewhere (5). The food consumed spontaneously by the controls determined the amounts weighed out for the "fatties," who generally consumed their allotments within one hour also. Thus both groups alternated between fed and fasting states, on the same time schedule. (B) Since the "fatty" is recognized by its ability to fatten, by the time experimental groups can be set up, the "fatty" has necessarily become fatter than its control. "Fatties" were therefore starved for 5 days to bring them down to the initial fat content of the lean. With allowance for the effect of an empty gut in the starved "fatties", it appeared that the fat content was normalized, both on the basis of how they looked, and on body weight in relation to leg or tail length. Two rats so prepared were sacrificed for determination of body composition, and found to have 8 and 14% fat, which is within the normal range for weanlings (6). Thus "fatties" were started on experiment 5 days older, and later than their controls. (C) It has been previously reported that "fatties" have a smaller skeleton and musculature than lean controls (4, 5). This stunting, amounting to 4% at 2 wk of age and rather more by weaning (4, 6), is statistically significant. For its smaller frame, the "fatty" is not entitled to as large a food allotment as its littermate control. Therefore the "fatties" were deliberately given only 85% as much food as was consumed by the controls. This factor was arrived at by measuring the food intake of younger lean rats matched in skeletal size (tail length) to the "fatties".

Energy calculations. The energy value assigned to L Sulfa was 4 kcal/g. Energy content of the rat carcasses was calculated as 3.2 (fat-free solids) + 9 (fat). This was arrived at in the following way. N × 6.25 is assumed to represent protein. Many observations in this laboratory show close proportionality between N and fat-free solids throughout life, so that one can substitute 0.8 (fat-free solids) for N × 6.25 as a measure of protein. Using this factor, and the standard factors of 4 kcal/g for protein and 9 kcal/g for fat, one derives the above calculation. Energy content of the rats at the start of the experiment were estimated by applying the same calculation to esti-

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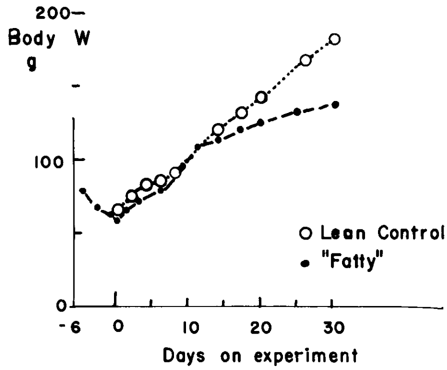

FIG. 1. Mean body weights of the six male pairs. Unless fasting, rats were weighed 1 or more hr after a meal. Initial age was 28 ± 3 days.

mated fat and fat-free solids contents. It was assumed that the experimental rats had the same % fat and % fat-free solids as the weanlings prepared in the same way but analyzed at that time.

Results. Typical weight curves—those for the six male pairs run for 30 days—are shown in Fig. 1. The large weight loss during starvation was only partly due to fat loss; it was also partly due to loss of intestinal contents, and this was of course promptly restored on refeeding. Lean controls became heavier than the "fatties", partly because they had more food, but partly also corresponding to the difference in composition of their weight gain; the weight value of 1 kcal in lean tissue with its associated water exceeds 1 g, while in the adipose tissue favored by the "fatty", the weight equivalent of 1 kcal is only ⅛ g. It is only when allowed to eat *ad libitum* that the "fatty" greatly exceeds the lean in weight.

Table I presents body composition and some energy values. This Table should be self-explanatory. "Fatties" were clearly fatter than normals, and retained in their bodies more of the energy which was supplied.

Discussion. The efficient performance of the "fatty" is established without the need for any assumptions or calculations; simply, while receiving less of the same diet as the controls, the "fatty" gets fatter. The magnitude of the discrepancy is 16.5 g excess fat in the short experiment, 42.5 g in the long experiment, or 0.55 and 0.57 g fat per day. Making the usual assumptions, this is about 5 kcal/day, or 1.25 g diet, well beyond any possible measurement error. The 15% reduction in food intake, imposed on the "fatties" because of their smaller frame size, is also about 5 kcal per day.

It is of interest to compare this rate of fattening with that of *ad libitum* fed rats, using published data for body fat (6) and growth (7). At weaning, males (*Fa/* and *fafa*) weigh 65 and 80 g, and have 7.5 and 18 g fat; 30 days later weights are 225 and 300, fat contents 18.2 and 98.4 g. The excess fat laid down per day by the "fatty" is 2.3 g, four times the rate with restricted feeding.

Some of the energy laid down as fat can be accounted for by the growth deficit, but not all. Unless one assumes enormous energy requirements for carrying out the synthetic processes of growth, enormous in relation to the energy requirements for the synthesis of fat, the growth deficit is too small to account for the fat excess. This is especially true for the long experiment, where the growth deficit is hardly greater than for the short experiment, while the fat excess is much greater. I have frequently alluded to the ability of the "fatty" to divert energy from growth to fat deposition, as though this were the key to the "fatty"'s problem (5, especially). It may well be the key to the special metabolic abnormality of the "fatty" genotype. But actually, as will be shown elsewhere,[2] it is possible to restore skeletal growth to normal in the "fatty" by the use of growth hormone, and "fatties" still lay down excessive fat. The source of this extra energy is of more interest for the general obesity problem.

The obvious possibility of reduced physical activity is being explored. So far, it appears that while *ad libitum* fed "fatties" are less active than normals, this is not so for "fatties" kept on a normal food intake, where activity in activity-measuring cages or in exercise wheels is as great as in the normal.[3] The possibility must be considered of some sort of difference in economy of motion in carrying out the same activity,

[2] Unpublished observations, L. M. Zucker. A MS is in preparation.

[3] Personal communication, 1974, P. R. Johnson, and J. Stern.

TABLE I
ENERGY UTILIZATION

Duration of Exp. d	Rat	N	Live W g	Fat g	Water g	Fat-free Solids g	Nitrogen g	Gain in energy kcal	Energy eaten kcal	% Energy retained
30	*fafa* ♂	6	137 ± 4.5[a]	28.6 ± 1.2	68.8 ± 2.4	24.6 ± 1.1	3.19 ± 0.14	208 ± 13	960 ± 5	21.5 ± 1.2
	Fa/ ♂	6	182 ± 8.1	12.1 ± 1.9	112.1 ± 1.5	40.1 ± 1.8	5.12 ± 0.23	89 ± 16	1128 ± 14	7.9 ± 1.5
74	*fafa* ♀	5	188 ± 5.9	73.6 ± 2.8	66.2 ± 2.5	25.6 ± 0.9		602 ± 15	2204 ± 57	26.8 ± 0.4
	Fa/ ♀	5	211 ± 6.9	31.1 ± 2.0	111.2 ± 4.1	43.1 ± 1.8		262 ± 7	2630 ± 105	10.0 ± 0.5

[a] Mean ± standard error of the mean.

but this is experimentally difficult to approach.

Bray and York (8) have found "fatties" to be moderately hypothyroid. PBI was low, radioactive iodine uptake and rate of release by the thyroid were both low in "fatties". Oxygen consumption (BMR) was also low (9). With closer effective coupling of work (ATP) and heat output, less heat and less energy expenditure accompanies the generation of the ATP necessary for the mechanical and chemical work of the body. This provides a possible explanation for the greater efficiency of energy utilization by the "fatty".

The prospect of finding a lower food intake which would prevent abnormal fattening is slight. In an experiment involving total starvation of young adults (6, especially Table V), 42 days of fasting cut the body weight in half, but % fat was still 38.1, far above the normal of 15–20%, although below the initial level of 45%. Obviously large-scale nonfat tissue loss has occurred, and the rat is still fat. It is clear that exploration of the region of greatly subnormal food intake involves cruel experimentation; a few trials indicate that the rats are in acute physiological distress, to the extent that two cases of tail eating took place. Total starvation is much less painful to endure. The "fatty" state certainly must be characterized as an intractable obesity.

Summary. The hereditarily obese rat "fatty", with food intake restricted to approximately normal, laid down excessive fat at the rate of 0.56 g rat per day for up to 74 days on experiment, producing an energy denser, but lighter weight, carcass than the normal control. The "fatty" retained over 20% of the energy supplied, in its carcass, the control less than 10%.

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