tion is about 6 mg%, and this ratio of 1 to some value greater than 10 is also reflected in the total activities shown above.

Since the rate of diffusion of these acids into blood seems to be slow, and since mechanisms for fixing carbon dioxide into organic acids in blood appear to be lacking, studies involving carbon dioxide fixation for the time intervals used above can be carried out *in vivo*, and yet each organ will synthesize its carbon-labeled organic acids appreciably uncontaminated by acids formed at another site in the same animal.

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Decreased Activity and Energy Balance in the Hereditary Obesity-Diabetes Syndrome of Mice[1, 2]

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The hereditary obesity-diabetes syndrome, previously described (*1, 2*), is a recessive Mendelian entity characterized by an adult weight up to three or four times the normal, sterility (*3*), atrophy and ulcers of the skin, and decreased life span. Histopathological studies (*4*) reveal considerably enlarged islets of Langerhans, with no other morphological evidence of endocrine disturbance. Total basal oxygen consumption is low (*5*), with basal metabolic rates 40–50% below normal. Radioiodine uptake is not decreased (*6*). Fasting respiratory quotients are normal, nonfasting respiratory quotients are high (*7*). The caloric intake of the obese mice (*1*) is about 25% higher than that of the nonobese. If the mice are allowed to select nutrients freely, the obese mice choose a higher proportion of fat and a lower proportion of carbohydrate than the nonobese. The animals become diabetic at about the tenth week of life (*2, 7*). The diabetes is characterized by extreme insulin resistance and sensitivity to the amount and the nature of the diet. The obese animals show a decreased ability to oxidize acetate fragments (*8*); these are deposited instead as fatty acids. The hyperglycemia appears to be due to a block of the hexokinase reactions secondary to this primary genetic block and induced by pituitary diabetogenic (growth) hormone (*7, 9*). This secondary block has been implicated in the etiology of the hyperphagia in the light of the glucostatic scheme of regulation of food intake (*10*).

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[2] As in previous studies, the mice used in these experiments were obtained through the kindness of Margaret M. Dickie, of the Jackson Memorial Laboratory, Bar Harbor, Me.

Obese animals are visibly less active than nonobese litter mates. It was the purpose of the study reported here to quantitate this difference in activity between obese and nonobese animals, and to see how it varied with age and degree of obesity. The contribution of this decrease in expenditure for work to the imbalance between energy intake and output could then be evaluated.

Thirty-six mice, 12 nonobese animals 4 months old, 12 obese litter mates, and 12 young (2 months) obese animals of the same weight as the nonobese were placed in activity (squirrel-type) cages equipped with wheels 36 cm in diameter rotating freely enough to prevent any climbing and to insure that all animals sat at the bottom of the wheel under comparable conditions. A counter registered the number of revolutions. The animals were fed Purina chow pellets and were allowed to drink water *ad lib*. The experiment lasted 21 days, with the number of revolutions recorded at 9:00 A.M. and 5:00 P.M. The rooms in which the animals were kept were maintained at constant temperature (24° C) and were illuminated from 9:00 A.M. to 5:30 P.M. Table I gives the starting weights, rates of weight change during the experimental period, average daily activity, and average daytime and nighttime activity rate of the obese, young obese, and nonobese animals.

TABLE 1*

	Obese (4 mo old)	Young obese (2 mo old)	Nonobese (4 mo old)
Starting wt (g)	51.2 ± 2.5	27.8 ± 3.0	26.9 ± 2.2
Wt variation (g/week)	+ 1.8 ± 0.9	+ 3.6 ± 1.4	− 1.2 ± 1.0
Total daily activity (rev/day)	74 ± 40	355 ± 233	4783 ± 1253
Daytime activity rate (rev/hr)	4 ± 2	14 ± 4	102 ± 5
Nighttime activity rate (rev/hr)	3 ± 2	13 ± 2	240 ± 32

* Starting weights, rates of weight change during experimental period, average daily activity and diurnal activity rhythm of obese, young obese, and nonobese mice. The values given are average (mean) values. The figures following ± are standard deviations.

It is immediately apparent that the difference in spontaneous activity between obese and nonobese animals is enormous. In fact, obese animals are practically inactive. This inactivity is not solely the result of extreme obesity but, in fact, precedes it, as is shown by the comparison of activity rates of nonobese animals and of young obese mice of the same weight. Incidental to this difference in average daily activity, the difference in activity rates during night (darkness) and day (illumination) conditions, very marked in nonobese animals, disappears in the obese. Although

nonobese animals, given the opportunity to exercise by being transferred to activity cages, lose some weight during the first 2 weeks (weight then stabilizes and activity rates decrease slightly), no such reaction is demonstrated by the young or the older obese animals. In much older animals not included in the main experiment (age over 8 months, weight over 60 g) the number of revolutions/day dropped to less than 2 or 3.

The fact that decrease in activity precedes marked obesity makes it possible to ascribe to this decrease in activity a role in the etiology of the obesity. The weight differences between obese and nonobese animals have been found to be accounted for almost exclusively by fat (*11*). Weight increases of 15–20 g/month in adult obese mice are frequently observed. The young obese mice in the experiment reported here, for example, were accumulating fat at the rate of 16 g/month. It is therefore readily seen that differences of food consumption between obese and nonobese animals of the order of 25% (*1*) can account for the development of the obesity only if the extra 5 calories/day consumed by the obese are converted into body fat with a net efficiency of about 100% instead of one of the order of 25%, as previously postulated. In some cases the increase in food intake over the nonobese level cannot *per se* account for the obesity. The explanation for this fact, as well as for the improbable efficiency level, lies in two findings: (*a*) The resting metabolism stays the same when the body weight increases by 200 or 300% (*5*); in fact, the total oxygen consumption per animal is somewhat lower in obese than in nonobese animals. (*b*) Far less energy is used in movement by the obese than by the nonobese animals, and the cost of moving the body weight does not increase as obesity develops because activity is almost nil. It can be calculated from respiratory data (*5*) that nonobese animals require 11 cal/day for basal expenditure. If specific dynamic action is taken as 10% of the total intake of 20 cal, it is readily seen that 7 cal are left for spontaneous activity and some fat formation. The same calculations applied to obese animals give 9.5 cal for basal expenditure, 2.5 for specific dynamic action, and 13 cal for fat formation and exercise, with the latter a negligible item. Decrease in activity therefore represents a not unimportant factor in the etiology of this form of obesity.

Two other observations are relevant to the problem of the relation of exercise to the development of obesity in these mice. First, when obese mice carry the waltzing gene and are in constant rotary movement in their cages, their weight rarely exceeds 40 g instead of twice that value. Second, it has been shown previously (*7*) that when obese mice are pair-fed with nonobese litter mates, their weight stabilizes at the level reached before paired feeding was started, neither increasing nor decreasing. As the resting over-all metabolism of obese animals is not greater than that of nonobese, they should, if their expenditure for work remained lower than that of the nonobese, still gain weight under paired feeding conditions. Actually, only a few mice do. The explanation of this apparent paradox lies in the fact that total or partial fasting increases the activity of obese mice proportionally much more than that of the nonobese. Total deprivation of food increases the number of revolutions per day by 50–60% for the nonobese—it brings it up to normal nonfasted levels (4000–5000) for young obese animals. Paired feeding, which represents a curtailment of intake of about 25% for the obese, is found to bring about a rate of activity of 1000–2000 revolutions per day. When the heavier weight of the obese animals is taken into account, the increase in work expenditure added to the decrease in caloric intake is seen to be sufficient to account for the cessation of weight increase.[3]

The relation of the decreased activity of the obese animals to their decreased resistance to cold is discussed in another publication (*12*), as is the relation of activity to human obesity (*13*).

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[3] In private conversation with Thomas H. Maren, of the American Cyanamid Co., it was found that he had independently arrived at the conclusion (unpublished) that part of the excess fat of the obese animals must be derived from energy devoted to exercise in the nonobese animals.

Mast Cells and Susceptibility to Experimental Atherosclerosis[1]

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It has been known for the past four decades that lipemia and atherosclerosis can be produced easily by cholesterol feeding in the rabbit, whereas the rat is a notoriously refractory species (*1*). The reason for the remarkable resistance of the latter species is unknown and has been the subject of considerable speculation. It has been attributed in turn to a very efficient vasa vasorum system, to a very low resting blood cholesterol

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