GENETIC ANALYSIS OF BROWN ADIPOSE TISSUE, OBESITY AND GROWTH IN MICE

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Manuscript received September 28, 1983

Revised copy accepted December 22, 1983

ABSTRACT

The hypothesis developed from single-gene mutant obese rodents that brown adipose tissue (BAT), through its thermogenic ability, is an important factor in the development of obesity, was tested in a randombred population of mice in which degree of adiposity is polygenically determined. Additive direct genetic parameters for measures of body size, lean, fatness and BAT at 6 wk of age were estimated under control and high-fat postweaning dietary regimens. Heritabilities were generally similar for the two diets. However, the lipid-free dry (LFD) component of BAT had a heritability estimate of 0.70 ± 0.26 on the control diet, but only 0.09 ± 0.20 on the high-fat diet. For all traits, genotype by diet interactions indicated that additive direct genetic rankings were not significantly different for the two diets. Based on estimates of genetic parameters in the control diet, selection for 6-wk body weight or 3- to 6-wk gain is expected to increase body size and adiposity. Selection for BAT weight is predicted to result in large, lean individuals. However, selection for the LFD content of BAT, generally believed to be a better indicator of thermogenic ability, is predicted to increase fatness as well as body size. Selection for LFD as a proportion of 6-wk body weight reduced the expected correlated response in fatness. It was concluded that BAT does not play a major role in determining the correlated response in obesity that is often found in populations selected for large body size.

MICE have been important animal models in the study of obesity in man (FESTING 1979). There has also been extensive use of laboratory rodents in studies concerning the improvement of domesticated animals by selection (ROBERTS 1979; YUKSEL 1979). An important goal in domestic species is the reduction of fat deposition. However, much of the research effort on the genetic basis of obesity has been expended on single gene mutant rodents (BRAY and YORK 1979), whereas human and other mammalian obesity is largely polygenic in origin (FOCH and MCCLEARN 1980; ALLEN and MCCARTHY 1980). The important concept that change in energy expenditure, either through metabolic rate or thermogenesis, rather than excess energy intake, causes obesity has been developed from studies in single-gene obese (*ob/ob*) mutant mice (JAMES and TRAYHURN 1976, 1981). Preliminary evidence in humans appears to support this idea (JAMES *et al.* 1979).

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Brown adipose tissue (BAT) has been implicated as a major determinant of energy expenditure differences in single-gene obese mice (TRAYHURN and JAMES 1981). BAT is distinguished from white adipose tissue by its larger number of mitochondria and lower lipid content (SMITH and HORWITZ 1969). The mitochondria of BAT have a unique protein (CANNON, HEDIN and NEDERGAARD 1982) that enables the production of relatively large amounts of heat (SMITH and HORWITZ 1969; NICHOLLS 1979). Defects in this function result in less energy expended as heat, thereby allowing more energy to become available for fat deposition (HOGAN and HIMMS-HAGEN 1980).

Evidence from rodents with obesity due to causes other than single genes supports the role of BAT in obesity. Ventromedial hypothalamic lesions that cause obesity also affect BAT function (ASSIMACOPOULOUS-JEANNET *et al.* 1981), and electrical stimulation of the ventromedial hypothalamus resulted in BAT heat production changes (PERKINS *et al.* 1981). Resistance to obesity induced by cafeteria feeding was correlated with amount of BAT (ROTHWELL, SAVILLE and STOCK 1982). Increase in oxygen consumption and weight of BAT following a single meal was observed by GLICK, TEAGUE and BRAY (1981). BAT is present in most mammalian species early in life (ROWLATT, MROSOVSKY and ENGLISH 1971), but its importance in adult animals, other than small rodents, is generally not known. BAT appears to be functional in adult humans (ROTHWELL and STOCK 1979; CONTALDO *et al.* 1981), but its relationship with obesity has not been established.

The purpose of the present research was to examine these ideas from a polygenic perspective. Very few estimates of genetic influence on obesity and BAT or genetic relationships between them have been reported. Polygenic obesity in animals is generally obtained by selection for increased growth or body size, with obesity being a correlated response to selection (MCCARTHY 1979). The importance of BAT in these observations will be examined. Both a high-fat and control diet will be used to compare genetic variation in a normal environment with a challenge environment expected to increase BAT mass and induce a thermogenic response.

MATERIALS AND METHODS

Albino mice (ICR) used in the experiment were obtained from the Institute for Cancer Research, Philadelphia, Pennsylvania and have been maintained as a closed, randombred population for approximately 70 generations in our laboratory. Sires were mated to three dams each, and litters were standardized to six males and two females when possible. During lactation, dams were fed Purina Mouse Chow. The laboratory was maintained at $22 \pm 2^\circ$ with a 12-hr light/12-hr dark cycle throughout the experiment.

At 3 wk of age, four males from each litter were weighed and then randomly assigned in pairs to either the control or high-fat diet (Table 1). The control diet was pelleted Purina Lab Chow, whereas the high-fat diet was ground Purina Mouse Chow with lard added to make a 22% fat diet. The high-fat diet was fed in small jars with lids to minimize waste and changed every 4 days to avoid spoilage. Food consumption was measured from age 3 to 6 wk on all pairs of full sibs for each diet.

At 6 wk of age, mice were weighed and killed for measurement of carcass traits. Right epididymal (EPID) and subcutaneous (SUBQ) fat-pads and pooled right and left interscapular BAT were excised and weighed. White fat surrounding BAT was carefully removed before weighing,

TABLE 1

Percent composition and metabolizable energy (ME) content of the diets

Component	Control diet	High-fat diet
Protein	23.4	15.4
Fat	4.5	22.0
Nitrogen-free extract	50.8	47.2
Fiber	5.0	2.0
Ash	7.3	4.8
ME (kcal/g)	3.4	4.5

and then BAT was stored frozen in sealed vials for later chemical analysis. The carcass was skinned and cut at the top of the sacral vertebrae and distally through the femurs where muscle ended. An estimate of carcass lean (LEAN) was given by removing surface fat from this hind section before weighing.

Chemical analysis of BAT was done with a continuous chloroform/methanol extraction apparatus described in more detail elsewhere (A.M. SAXTON, E. J. EISEN and J. M. LEATHERWOOD, unpublished results). Lipid-free dry (LFD) tissue and dry lipid content of BAT were obtained.

Data were analyzed within diets by a nested random model including the effects of sire, dam within sire and error. Analyses of variance and covariance for unbalanced data were used to obtain estimates of variance and covariance components (BECKER 1975). To give some idea of the degree of unbalance, it would have been possible to discard 97 of the 1017 observations to yield two completely balanced data sets, one with 52 sires (two dams each) and one with 42 sires (three dams each). The total number of sires was 101.

Genotype by environment interactions were analyzed using a model including the effects of diet, sire, dam within sire, respective interactions with diet and error. Variance and covariance components were estimated by Henderson's method III (SEARLE 1971).

A genetic model including additive direct (V_A), dominance (V_D), "maternal" (V_M = additive maternal genetic, maternal environment and additive direct-maternal covariance) and within family environmental (V_E) variances was assumed. Epistatic variance was assumed to be zero. BECKER (1975) gives methods for estimating heritabilities and additive genetic correlations for the within diet analyses. In addition, maternal plus one-quarter dominance variances and covariances were estimated by dam minus sire components. These were then used to estimate maternal parameters analogous to the additive direct genetic parameters. WILLHAM (1963) discusses the contribution of maternal effects to covariance between relatives.

Within diets, the proportion of variance due to additive direct effects was estimated by heritability as

$$h_i^2 = \frac{4V_{s_i}}{V_{s_i} + V_{d_i} + V_{e_i}}$$

and the proportion due to maternal plus one-fourth dominance effects as

$$M_i = \frac{V_{d_i} - V_{s_i}}{V_{s_i} + V_{d_i} + V_{e_i}}$$

where i represents one of the two diets. Genetic correlations for the same trait in two environments were estimated from the genotype by environment analysis using methods discussed by YAMADA (1962). For additive direct effects the formula used was

$$r_G = V_s / (V_s + V'_{gf}),$$

where $V'_{gf} = V_{gf} - 1/2(V_{s1}^{1/2} - V_{s2}^{1/2})^2$ is corrected for bias due to different additive variance in the two diets. Heritability estimates across diets were calculated by

$$h^2 = \frac{4V_s}{V_s + V_{sf} + V_d + V_{df} + V_e}$$

In the preceding formulas, V represents a variance component, with subscripts indicating sire (s), dam (d), their interactions with diet (sf , df) and error (e) sources of variance. Analogous formulas were used in estimating parameters involving maternal plus one-quarter dominance effects.

Standard errors of the estimates were calculated assuming independence of mean squares. Variances of ratios were approximated by $\text{Var}(X/Y) \cong (X^2 \text{Var}(Y) + Y^2 \text{Var}(X) - 2XY \text{Cov}(X,Y))/Y^4$. Variances of functions involved in calculating genetic correlations were developed from the discussion of TALLIS (1959).

Because feed consumption was measured on pairs of full sibs, the dam within sire and error components are confounded for this trait. Sire components have the usual genetic interpretation, but the phenotypic variance, estimated by twice the within sire component, has expectation

$$V_A + 2V_M + 1.25V_D + V_E.$$

Thus, heritabilities and phenotypic correlations involving consumption will be biased.

Genetic change in the mean of traits under artificial selection was estimated by

$$\Delta_{ji} = kh_i h_j r_{Aij} V_{Pj}^{1/2}$$

where Δ_{ji} is the change in trait j due to selection on trait i , k is the selection intensity, h_i and h_j are the square roots of the heritabilities for traits i and j , r_{Aij} is the additive genetic correlation between traits i and j and V_{Pj} is the phenotypic variance for trait j .

RESULTS

Means and phenotypic standard deviations for the traits of interest are given in Table 2. Most traits were increased after 3 wk on the high-fat diet ($P < 0.01$). An exception was feed consumption, with animals on high fat eating less ($P < 0.01$). However, converting to energy intake by use of values in Table 1 resulted in a nonsignificant increase of 1.91 kcal/day for animals on high fat. Regulation of energy intake was also seen in a previous experiment (A. M. SAXTON, E. J. EISEN and J. M. LEATHERWOOD, unpublished results). Utilization of the high-fat diet must have been more efficient for these animals to have increased fat and body weight without having increased energy intake. Alternatively, presentation of the diets in different physical form may have indirectly caused differences in caloric utilization.

Additive direct and maternal variances as percentages of the phenotypic variance are given in Table 3. Maternal parameter estimates are biased by maternal environmental variance and one-fourth of the dominance variance. The known importance of maternal effects on growth and obesity in mice, even at 6 wk of age (MOORE, EISEN and ULBERG 1970; HAYES and EISEN 1979; EISEN and ROBERTS 1981), makes it unwise to consider four times the maternal component as an indicator of the importance of dominance effects. Heritability estimates within each environment are used to predict response to selection within an environment and include the genotype $\times$ environment variance in the numerator. Heritability estimates across diets provide estimates of the proportion of additive genetic variance unbiased by genotype $\times$ environment variance.

There were no significant differences in heritabilities between the control and high-fat diets. However, some of the changes were interesting. Heritabil-

TABLE 2

Means and phenotypic standard deviations in the two environments^a

Trait	Control diet (n = 520)		High-fat diet (n = 497)	
	Mean	Phenotypic SD	Mean	Phenotypic SD
3-wk wt (g)	15.12	1.75	15.09	1.82
6-wk wt (g)	31.39	2.70	34.71	2.83
Gain (g)	16.26	2.25	19.62	2.06
EPID (mg)	162	61.2	343	128.5
SUBQ (mg)	111	25.1	172	48.0
BAT (mg)	77	15.5	145	31.1
LEAN (g)	3.58	0.43	4.39	0.39
LFD (mg)	9.69	1.60	14.30	2.20
BAT lipid (mg)	41	11.0	91	25.3
LFD/6-wk wt (100 mg/g)	31.0	5.1	41.3	6.1
Consumption ^b (g/day/mouse)	5.83	0.65	4.83	0.56

^a All trait means except 3-wk wt differ across diets ($P < 0.01$).^b Numbers of observations were 257 and 242, respectively. Phenotypic standard deviations are biased upward as described in the text.

TABLE 3

Relative importance of genetic differences within and across diets^a

Trait	Control diet		High-fat diet		Across diets		r_G	
	h_i^2	M_i	h_i^2	M_i	h^2	M	Additive	Maternal
3-wk wt	10	57	25	51	5	56	29	103
6-wk wt	37	25	43	24	39	7	98	27*
Gain	44	28	54	10	56	-6	117	-34*
EPID	17	37	38	23	17	17	83	90
SUBQ	38	19	17	25	9	11	38	60
BAT	23	19	17	15	11	17	66	130
LEAN	40	37	33	35	35	13	98	137*
LFD	70	4	9	27	30	4	117	26*
BAT lipid	0.5	33	19	15	6	16	167	108
LFD/6-wk wt	39	23	16	24	31	1	124	5*
Consumption	39 ^b		42 ^b		25 ^b		65	
SE range	19-26	10-18	15-27	11-18	12-20	5-8	32-86	7-50

^a h_i^2 estimates additive variance, and M_i estimates maternal variance plus one-fourth dominance variance within diets expressed as a percent of phenotypic variance. h^2 and M are corresponding estimates across diets. r_G is the genetic correlation of the same trait across diets. All estimates multiplied by 100.^b Estimates are biased down. See text for details.* Estimates significantly different from 1 ($P < 0.05$).

ities for SUBQ and EPID reversed ranking in the two environments. Expressing the fat-pads as a percent of 6-wk body weight had little effect on the results (not shown). Heritability for LFD was low on high fat but very high in the control environment. BAT lipid estimates had the opposite trend, with essentially no additive variance in the control diet. Maternal effects were largest for 3-wk weight, as might be expected.

The heritabilities for most of the traits indicate that artificial selection would be effective in changing the mean of the population on either diet. It is of interest next to ask whether the same genetic change (proportional to heritability) due to selection on one diet would occur if animals were raised on the other diet. Analyses of genotype by environment interaction were used to examine this question (Table 3). None of the additive correlations was significantly different from 1. However, the genetic correlation for SUBQ was small. A previous study found that SUBQ may respond differently to high-fat diets (DEODATO, EISEN and LEATHERWOOD 1982). Several maternal correlations were significantly less than 1. These demonstrate that changes in maternal or dominance effects in one environment would not change performance on the other diet to a similar extent.

Additive genetic correlations among traits for each diet are given in Table 4. In general, there was very little difference in estimates between diets. The lack of additive variance for BAT lipid on the control diet resulted in unrealistic estimates. Additive correlations for LFD per unit of body weight had a tendency to be positive on the control diet and negative on high fat, perhaps due, in part, to changes in amount of additive genetic variance for LFD (Table 3).

The large positive additive genetic correlation between 3- to 6-wk weight agreed with previous results for correlations among weights at different ages (HANRAHAN and EISEN 1974). Weaning weight was negatively correlated with fat-pad weights and had little correlation with BAT traits. Selection for 3-wk weight would apparently result in increased body weight but less fat. Gain and 6-wk weight were highly correlated with both white and brown adipose measures. Correlation between the two white fat depots was large, indicating a common genetic mechanism for fat accretion in the two depots. Correlations of white with brown adipose measures were generally smaller. Correlations among BAT traits were very large. Expressing LFD per unit of body weight resulted in negative correlations, as might be expected, but these were very small. Consumption had large positive correlations with measures of body size, moderate correlations with BAT traits and surprisingly little correlation with white fat.

Due to the similarity for each diet, only pooled estimates are given (Table 4) of phenotypic correlations. Phenotypic correlations were positive and moderate in size, except for LFD per body weight, where body weight in the denominator caused small negative correlations. Phenotypic correlation of gain with 3-wk weight was essentially zero.

Responses to selection make interpretation of the additive direct genetic parameters easier (Table 5). Only single-trait selection is presented since choosing meaningful economic weights for index selection is difficult. Influence of maternal effects on selection response had to be ignored because additive maternal genetic variance and the covariance between additive direct and additive maternal effects could not be estimated separately. Emphasis here is placed on response with the control diet; therefore, heritabilities, additive genetic correlations and phenotypic variances in that environment were used. Due to the lack of additive variance, BAT lipid was not used in the analysis.

TABLE 4. Additive genetic correlations $\pm$ SE for the two diets (above diagonal) and pooled phenotypic correlations (below diagonal)^a

Trait	3-wk wt	6-wk wt	Gain	EPID	SUBQ	LEAN	BAT	BAT lipid	LFD	LFD/wt	Consumption
3-wk wt		45 $\pm$ 61 60 $\pm$ 30	12 $\pm$ 82 14 $\pm$ 45	-175 $\pm$ 340 -46 $\pm$ 81	-6 $\pm$ 86 -26 $\pm$ 96	74 $\pm$ 57 142 $\pm$ 41	-44 $\pm$ 142 6 $\pm$ 75	^b 19 $\pm$ 67	20 $\pm$ 60 -6 $\pm$ 106	3 $\pm$ 81 -54 $\pm$ 70	78 $\pm$ 135 76 $\pm$ 44
6-wk wt	63		94 $\pm$ 14 88 $\pm$ 12	41 $\pm$ 46 32 $\pm$ 34	20 $\pm$ 38 51 $\pm$ 40	85 $\pm$ 11 65 $\pm$ 22	56 $\pm$ 36 60 $\pm$ 37	^b 71 $\pm$ 32	79 $\pm$ 28 25 $\pm$ 69	54 $\pm$ 54 -66 $\pm$ 55	56 $\pm$ 41 72 $\pm$ 37
Gain	-2	76		110 $\pm$ 60 68 $\pm$ 25	24 $\pm$ 36 79 $\pm$ 42	66 $\pm$ 26 -6 $\pm$ 43	79 $\pm$ 42 71 $\pm$ 36	^b 77 $\pm$ 33	81 $\pm$ 28 34 $\pm$ 62	59 $\pm$ 50 -49 $\pm$ 54	36 $\pm$ 34 35 $\pm$ 30
EPID	43	60	41		69 $\pm$ 31 73 $\pm$ 26	7 $\pm$ 65 -33 $\pm$ 60	-10 $\pm$ 89 26 $\pm$ 51	^b 34 $\pm$ 45	47 $\pm$ 45 4 $\pm$ 80	46 $\pm$ 72 -25 $\pm$ 60	-10 $\pm$ 58 -7 $\pm$ 35
SUBQ	34	50	36	73		7 $\pm$ 41 -28 $\pm$ 82	-11 $\pm$ 59 70 $\pm$ 49	^b 64 $\pm$ 45	15 $\pm$ 29 80 $\pm$ 112	12 $\pm$ 40 19 $\pm$ 89	-27 $\pm$ 36 5 $\pm$ 44
LEAN	66	82	50	43	30		17 $\pm$ 48 13 $\pm$ 61	^b 31 $\pm$ 54	49 $\pm$ 29 -26 $\pm$ 103	19 $\pm$ 46 -73 $\pm$ 64	48 $\pm$ 45 58 $\pm$ 40
BAT	29	51	41	57	57	32		^b 102 $\pm$ 5	118 $\pm$ 28 97 $\pm$ 46	138 $\pm$ 52 23 $\pm$ 76	-4 $\pm$ 40 18 $\pm$ 53
BAT lipid	31	53	42	64	65	32	96		^b 115 $\pm$ 76	^b 28 $\pm$ 72	^b 34 $\pm$ 45
LFD	14	30	26	23	23	21	71	36		94 $\pm$ 8 56 $\pm$ 67	21 $\pm$ 28 -41 $\pm$ 60
LFD/6-wk wt	-20	-24	-14	-9	-5	-22	43	26	85		-6 $\pm$ 38 -71 $\pm$ 40
Consumption	50	58	28	30	26	54	36	34	28	-4	

^a First value for genetic correlations is for the control diet, and second value is for the high-fat diet. Estimates multiplied by 100. SE for phenotypic correlations ranged from 2 to 5.^b Estimates meaningless due to low additive variance for BAT on the control diet.

TABLE 5
Predicted direct and indirect responses to genetic selection^a

Trait selected	Response									
	3 wk wt	6 wk wt	Gain	EPID	SUBQ	LEAN	BAT	LFD	LFD/wt	Consumption
3-wk wt	1.16	24	6	-134	-3	37	-29	8	2	40
6-wk wt	87	3.18	86	60	20	82	71	57	53	54
Gain	25	103	6.09	177	26	69	109	64	63	38
EPID	-228	28	68	6.44	46	5	-9	23	30	-7
SUBQ	-12	20	22	103	8.59	7	-14	11	12	-27
LEAN	148	88	63	11	7	4.81	22	37	19	49
BAT	-67	44	57	-12	-9	13	4.64	68	106	-3
LFD	53	109	102	95	20	65	206	11.53	126	28
LFD/6-wk wt	6	55	56	70	12	19	180	70	6.41	17
Consumption	154	58	34	-15	-27	47	-5	16	-5	4.33

^a Direct responses are on the diagonal, and change is expressed as a percent of the mean. Selection intensity is 1. Indirect responses are given as a percent of the direct response. Estimates used in predicting selection response are control diet values.

Selection for increased 3-wk weight, BAT or consumption is predicted to result in increased body size with decreased white fat. It must be emphasized that the results are dependent on genetic correlations with large standard errors; therefore, actual response in white fat could be zero or even positive. Selection for LEAN is predicted to be effective at increasing body size with only a slight increase in white fat. Selection for gain or SUBQ are predicted to be the most effective means of increasing both EPID and SUBQ, but selection for SUBQ is expected to increase LEAN and body weight less than selection for gain. Selection for BAT is expected to result in moderate decreases in fatness and consumption with some increase in body size. Indirect selection for BAT by either LFD or LFD per body weight would be most effective in increasing BAT. However, direct selection for LFD variables also would be expected to increase fatness, particularly EPID.

DISCUSSION

This study examined the quantitative genetic relationship among growth, adiposity and BAT in a randombred population of mice. Heritability estimates for white fat based on covariances of relatives were moderate in size and smaller than a realized estimate of 0.6 from a mouse selection study (HÖRSTGEN 1978) and estimates between 0.4 and 0.5 reported in mice (HORST *et al.* 1979) and other species (McCARTHY 1979). Differences in fat-pad weights among lines selected for size or growth have been partitioned into additive direct and maternal genetic effects (EISEN and ROBERTS 1981; DEODATO, EISEN and LEATHERWOOD 1982). Additive effects were large, but maternal effects were also sizable. The importance of maternal effects was also seen in this study if dominance contributions are assumed to be negligible. The large additive genetic correlation between EPID and SUBQ depots indicates that changing the distribution of fat would be difficult, but sufficient genetic variability remained in one depot after adjustment for the second depot so as to make selection for a change in fat distribution feasible.

Most of the estimates involving growth, body size and consumption were comparable to previous results in mice and other species (SUTHERLAND *et al.* 1970; JARA-ALMONTE and WHITE 1973). However, the prediction that selection for 3-wk weight or consumption would decrease fatness was surprising. These predictions may be the result of sampling errors in estimating the genetic correlations. The phenotypic correlations between fat-pad weights and feed consumption and between fat-pad weights and 3-wk body weight were positive, in contrast to the negative genetic correlations. It is a fairly common observation that phenotypic and genetic correlations for growth and carcass traits in extensive data sets are usually similar. This interpretation is compatible with several selection studies. SUTHERLAND, BIONDINI and WARD (1974) selected a line for increased consumption, and increased adiposity was a correlated response. Selection for body size at early ages is expected to increase fatness at later ages according to the hypothesis of HAYES and McCARTHY (1976). HULL (1960) and BAKER, CARTER and COX (1979) observed that a line

selected for large 3-wk body weight was the fattest at 6 wk of age when compared with lines selected for body weight at later ages.

The main purpose of this research was to examine the suggestion that BAT may be involved in obesity. This idea has been supported by studies in other types of animal models but has not been examined in polygenic adiposity models. Estimates of genetic parameters have been reported for LFD per body weight after cold adaptation (LACY and LYNCH 1979; LYNCH and SULZBACH 1984), which may have an effect similar to high-energy diets (ROTHWELL and STOCK 1980). The heritability estimates of 0.08 ± 0.06 in a heterogeneous population (LACY and LYNCH 1979) and 0.09 ± 0.05 from a diallel cross of inbred lines (LYNCH and SULZBACH 1984) agree with results from the high-fat diet. In contrast, heritability without an environmental challenge was much higher in the present study. A possible explanation for the difference is that additive variance for LFD weight in the control diet may be due to a small number of genes the expression of which is required under a high-fat diet or chronic cold challenge. This leads to speculation that regulatory genes may be responsible for the additive variance in LFD under the control diet. Selection in the control environment may initially result in rapid responses, but, as the population mean approaches that in the challenge environment, response may cease. Such a physiological limit to size of BAT is suggested by the prediction that selection for BAT in the challenge environment would not be effective. Age at first estrus in mice appears to follow this pattern (DRICKAMER 1981a,b).

Genetic correlations from the diallel cross of inbred lines (SULZBACH and LYNCH 1984) were in agreement with present estimates from the challenge environment, except that the correlation of LFD per body weight with consumption was negative here. The genetic correlations between LFD/6-wk body weight and 6-wk body weight or gain were negative on the high-fat diet but positive on the control diet. C. B. LYNCH (personal communication) found a similar negative genetic correlation between LFD per body weight and body weight in cold-acclimated mice, again suggesting a parallel between the effects of cold adaptation and a high-energy diet on LFD per body weight. The positive genetic correlation observed on the control diet is probably due to sampling because selection for growth rate on a control-type diet has caused negative correlated responses in LFD per body weight (A. M. SAXTON, E. J. EISEN and J. M. LEATHERWOOD, unpublished results; C. B. LYNCH, personal communication). These estimates argue for a genetic association between large LFD depots and smaller body and white adipose weights, as would be expected if LFD were involved in converting energy to heat and reducing energy deposition as fat or lean tissue. However, the use of LFD per unit of body weight may be misleading. Due to the automatic negative correlation between a quantity and its inverse (SUTHERLAND 1965), it is difficult to say whether the observed negative correlations in the challenge environment have biological meaning or are statistical artifacts. In support of the latter conclusion, genetic correlations with LFD alone were mostly positive.

Further evidence supporting this conclusion comes from a study of correlated responses in LFD at 6 and 12 wk of age on either a high-fat or control

diet in two lines selected for rapid growth rate (H_6 and M_{16}) and a slow growth line (L_6) (A. M. SAXTON, E. J. EISEN and J. M. LEATHERWOOD, unpublished results). When LFD was adjusted by covariance analysis for body weight, the only groups showing a negative correlated response in LFD were M_{16} at 6 wk on both diets and H_6 at 12 wk on the control diet, whereas M_{16} on the high-fat diet at 12 wk had a positive correlated response. The other eight groups showed no significant correlated response in LFD at a constant body weight.

Although causality cannot be inferred from correlations, predicted selection responses showed important relationships. Selection for gain is predicted to increase growth, fatness and BAT measures. Selection for gain in the ICR population has resulted in an obese line (EISEN *et al.* 1978), and measures of BAT were increased in this line (A. M. SAXTON, E. J. EISEN and J. M. LEATHERWOOD, unpublished results). Of most interest here is the prediction that selection for increased BAT would decrease fatness. This agrees with the hypothesis that BAT metabolizes energy stores and, thus, acts to decrease adiposity. However, LFD is generally believed to be a better indicator of thermogenic capacity (A. M. SAXTON, E. J. EISEN and J. M. LEATHERWOOD, unpublished results). Based on parameter estimates in the present study, selection for LFD or LFD per body weight is expected to increase fatness, which places doubt on the BAT predictions. Also, increasing BAT through indirect selection on LFD is expected to be twice as effective as direct selection for BAT, but, again, fatness is expected to increase. It is concluded that BAT is not a major component in determining the degree of polygenically controlled obesity.

Caution should be used in considering BAT or LFD weight as a measure of ability to perform a biochemical function. An example is the single-gene obese (*ob/ob*) mouse, which may have more BAT than its lean siblings, but in which mitochondrial function is abnormal (HOGAN and HIMMS-HAGEN 1980). However, several authors support the use of LFD (CHAFFEE and ROBERTS 1971; ROTHWELL, SAVILLE and STOCK 1982). Additionally, SULZBACH and LYNCH (1984) found a significant additive genetic correlation between LFD per body weight and oxygen consumption, a more established measure of thermogenic ability.

Paper no. 9003 of the Journal Series of the North Carolina Agricultural Research Service, Raleigh, North Carolina. The use of trade names in this publication does not imply endorsement by the North Carolina Agricultural Research Service of the products named nor criticism of similar ones not mentioned.

LITERATURE CITED

- ALLEN, P. and J. C. MCCARTHY, 1980 The effects of selection for high and low body weight on the proportion and distribution of fat in mice. *Anim. Prod.* **31**: 1-11.
- ASSIMACOPOULOUS-JEANNET, F., L. GIRARDIER, F. ROHNER-JEANREAUD and J. SEYDOUX, 1981 Reactivation of brown adipose tissue in hypothalamic lesioned rats by food restriction or cold exposure. *J. Physiol. (Lond.)* **318**: 60P-61P.
- BAKER, R. L., A. H. CARTER and E. H. COX, 1979 The effect of selection for body weight at different ages on fat deposition in mice. *NZ Soc. Anim. Prod.* **39**: 118-128.
- BECKER, W. A., 1975 *Manual of Quantitative Genetics*, Ed. 3. Washington State University Press, Pullman, Washington.

- BRAY, G. A. and D. A. YORK, 1979 Hypothalamic and genetic obesity in experimental animals: an autonomic and endocrine hypothesis. *Physiol. Rev.* **59**: 719–809.
- CANNON, B., A. HEDIN and J. NEDERGAARD, 1982 Exclusive occurrence of thermogenin antigen in brown adipose tissue. *FEBS Lett.* **150**: 129–132.
- CHAFFEE, R. R. J. and J. C. ROBERTS, 1971 Temperature acclimation in birds and mammals. *Annu. Rev. Physiol.* **33**: 155–197.
- CONTALDO, F., E. PRESTA, G. DI BIASE, L. SCALFI, M. MANCINI, G. MADDALENA, O. DI DIVITIIS and P. ROCCO, 1981 Preliminary evidence for brown fat defect in human obesity. pp. 143–146. In: *The Body Weight Regulatory System: Normal and Disturbed Mechanisms*, Edited by L. A. CIOFFI, W. P. T. JAMES and T. B. VAN ITALLIE. Raven Press, New York.
- DEODATO, A. DE P., E. J. EISEN and J. M. LEATHERWOOD, 1982 Additive, nonadditive and maternal genetic effects on adiposity in mice fed different levels of fat. *Can. J. Genet. Cytol.* **24**: 347–360.
- DRICKAMER, L. C., 1981a Selection for age of sexual maturation in mice and the consequences for population regulation. *Behav. Neural Biol.* **31**: 82–89.
- DRICKAMER, L. C., 1981b Acceleration and delay of sexual maturation in female house mice previously selected for early and late first vaginal oestrus. *J. Reprod. Fertil.* **63**: 325–329.
- EISEN, E. J., J. F. HAYES, C. E. ALLEN, H. BAKKER and J. NAGAI, 1978 Cellular characteristics of gonadal fat pads, livers and kidneys in two strains of mice selected for rapid growth. *Growth* **42**: 7–25.
- EISEN, E. J. and R. C. ROBERTS, 1981 Postnatal maternal effects on growth and fat deposition in mice selected for large and small size. *J. Anim. Sci.* **53**: 952–965.
- FESTING, M. F. W., 1979 The inheritance of obesity in animal models of obesity. pp. 15–37. In: *Animal Models of Obesity*, Edited by M. F. W. FESTING. MacMillan Press, London.
- FOCH, T. T. and G. E. MCCLEARN, 1980 Genetics, body weight and obesity. pp. 48–71. In: *Obesity*, Edited by A. J. STUNKARD. W. B. Saunders, Philadelphia, Pennsylvania.
- GLICK, Z., R. J. TEAGUE and G. A. BRAY, 1981 Brown adipose tissue: thermic response increased by a single low protein, high carbohydrate meal. *Science* **213**: 1125–1127.
- HANRAHAN, J. P. and E. J. EISEN, 1974 Genetic variation in litter size and 12-day weight in mice and their relationships with post-weaning growth. *Anim. Prod.* **19**: 13–23.
- HAYES, J. F. and E. J. EISEN, 1979 Direct genetic and postnatal maternal genetic effects on body composition in mice selected for body weight. *Can. J. Genet. Cytol.* **21**: 43–56.
- HAYES, J. F. and J. C. MCCARTHY, 1976 The effects of selection at different ages for high and low body weight on the pattern of fat deposition in mice. *Genet. Res.* **27**: 389–403.
- HOGAN, S. and J. HIMMS-HAGEN, 1980 Abnormal brown adipose tissue in obese (ob/ob) mice: response to acclimation to cold. *Am. J. Physiol.* **239**: E301–E309.
- HORST, P., D. STEINHAUF, J. H. WENINGER, E. S. TAWFIK and F. MAJOR, 1979 Preliminary selection results for the combination of total protein deposition and endurance in mice. *Z. Tierzuchtg. Zuchtgsbiol.* **96**: 221–234.
- HÖRSTGEN, G., 1978 Modellversuch mit Mäusen zur genetischen Differenzierung von Zuchtlinien durch Selektion für quantitative Merkmale. Ph.D. Thesis, Institut für Tierzucht und Haustiergenetik, University of Göttingen, Federal Republic of Germany.
- HULL, P., 1960 Genetic relations between carcass fat and body weight in mice. *J. Agric. Sci.* **55**: 317–321.
- JAMES, W. P. T., M. J. DAUNCEY, R. T. JUNG, P. S. SHETTY and P. TRAYHURN, 1979 Comparison of genetic models of obesity in animals with obesity in man. pp. 221–235. In: *Animal Models of Obesity*, Edited by M. F. W. FESTING. MacMillan Press, London.

- JAMES, W. P. T. and P. TRAYHURN, 1976 An integrated view of the metabolic and genetic basis for obesity. *Lancet* **2**: 770-773.
- JAMES, W. P. T. and P. TRAYHURN, 1981 Thermogenesis and obesity. *Br. Med. Bull.* **37**: 43-48.
- JARA-ALMONTE, M. and J. M. WHITE, 1973 Genetic relationships among milk yield, growth, feed intake and efficiency in laboratory mice. *J. Anim. Sci.* **37**: 410-416.
- LACY, R. C. and C. B. LYNCH, 1979 Quantitative genetic analysis of temperature regulation in *Mus musculus*. I. Partitioning of variance. *Genetics* **91**: 743-753.
- LYNCH, C. B. and D. S. SULZBACH, 1984 Quantitative genetic analysis of temperature regulation in *Mus musculus*. II. Diallel analysis of individual traits. Evolution. In press.
- MCCARTHY, J. C., 1979 Normal variation in body fat and its inheritance. pp. 1-14. In: *Animal Models of Obesity*, Edited by M. F. W. FESTING. MacMillan Press, London.
- MOORE, R. W., E. J. EISEN and L. C. ULBERG, 1970 Prenatal and postnatal maternal influences on growth in mice selected for body weight. *Genetics* **64**: 59-68.
- NICHOLLS, D. G., 1979 Brown adipose tissue mitochondria. *Biochim. Biophys. Acta* **549**: 1-29.
- PERKINS, M. N., N. J. ROTHWELL, M. J. STOCK and T. W. STONE, 1981 Activation of brown adipose tissue thermogenesis by the ventromedial hypothalamus. *Nature* **289**: 401-402.
- ROBERTS, R. C., 1979 Side effects of selection for growth in laboratory animals. *Livest. Prod. Sci.* **6**: 93-104.
- ROTHWELL, N. J., M. E. SAVILLE and M. J. STOCK, 1982 Effects of feeding a "cafeteria" diet on energy balance and diet-induced thermogenesis in four strains of rat. *J. Nutr.* **112**: 1515-1524.
- ROTHWELL, N. J. and M. J. STOCK, 1979 A role for brown adipose tissue in diet-induced thermogenesis. *Nature* **281**: 31-35.
- ROTHWELL, N. J. and M. J. STOCK, 1980 Similarities between cold- and diet-induced thermogenesis in the rat. *Can. J. Physiol. Pharmacol.* **58**: 842-848.
- ROWLATT, U., N. MROSOVSKY and A. ENGLISH, 1971 A comparative survey of brown fat in the neck and axilla of mammals at birth. *Biol. Neonate* **17**: 53-83.
- SEARLE, S. R., 1971 Topics in variance component estimation. *Biometrics* **27**: 1-76.
- SMITH, R. E. and B. A. HORWITZ, 1969 Brown fat and thermogenesis. *Physiol. Rev.* **49**: 330-425.
- SULZBACH, D. S. and C. B. LYNCH, 1984 Quantitative genetic analysis of temperature regulation in *Mus musculus*. III. Diallel analysis of correlations between traits. Evolution. In press.
- SUTHERLAND, T. M., 1965 The correlation between feed efficiency and rate of gain, a ratio and its denominator. *Biometrics* **21**: 739-749.
- SUTHERLAND, T. M., P. E. BIONDINI, L. H. HAVERLAND, D. PETTUS and W. B. OWEN, 1970 Selection for rate of gain, appetite and efficiency of feed utilization in mice. *J. Anim. Sci.* **31**: 1049-1057.
- SUTHERLAND, T. M., P. E. BIONDINI and G. M. WARD, 1974 Selection for growth rate, feed efficiency and body composition in mice. *Genetics* **78**: 525-540.
- TALLIS, G. M., 1959 Sampling errors of genetic correlation coefficients calculated from analyses of variance and covariance. *Aust. J. Stat.* **1**: 35-43.
- TRAYHURN, P. and W. P. T. JAMES, 1981 Thermogenesis: dietary and non-shivering aspects. pp. 97-105. In: *The Body Weight Regulatory System: Normal and Disturbed Mechanisms*, Edited by L. A. CIOFFI, W. P. T. JAMES and T. B. VAN ITALLIE. Raven Press, New York.

- WILLHAM, R. L., 1963 The covariance between relatives for characters composed of components contributed by related individuals. *Biometrics* **19**: 18-27.
- YAMADA, Y., 1962 Genotype by environment interaction and genetic correlation of the same trait under different environments. *Jpn. J. Genet.* **37**: 498-509.
- YUKSEL, E., 1979 Genetic aspects of the efficiency of food utilisation in some farm and laboratory animals. *Anim. Breed. Abst.* **47**: 499-504.

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