Quantitative Genetics of Transgenic Mice: Components of Phenotypic Variation in Body Weights and Weight Gains

A. C. Clutter,* D. Pomp*¹ and J. D. Murray[†]

*Department of Animal Science, Oklahoma State University, Stillwater, Oklahoma 74078-0425 and [†]Department of Animal Science and Department of Population Health and Reproduction, School of Veterinary Medicine, University of California, Davis, California 95616-8521

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ABSTRACT

Transgenic mice possessing an ovine growth hormone gene were used to study the effects of elevated growth hormone on quantitative genetic variation. Males hemizygous for the transgene were mated to wild-type females to produce half- and full-sib families in which approximately half the progeny were transgenic and half were wild type. Analyses of body weights at 3–10 weeks, and weight gains from 3 to 6, and 6 to 10 weeks produced estimates of the proportion of total variance due to additive genetic effects (h^2) and common litter effects (c^2), and the genetic correlation between transgenic and wild-type expression of each trait. At 10 weeks, body weight of transgenics exceeded that of wild types by 26 and 49% in males and females, respectively. Estimated genetic variances in the transgenic group were significantly greater than zero for body weights at most ages and for both measurements of gain. Common litter effects accounted for a similar proportion of variation in the wild-type and transgenic groups. Additive genetic correlations between wild-type and transgenic expression of body weights tended to decline with age, indicating that a partially different array of genes may have begun to affect body weight in the transgenic group.

IN recent years, a large body of work with transgenic mice, sheep and pigs (PALMITER *et al.* 1982; PURSEL *et al.* 1990; NANCARROW *et al.* 1991; POMP *et al.* 1992) has revealed that the effects of growth hormone transgenes on various metabolic and developmental processes may have great potential value in livestock production applications. Exogenous treatments with growth hormone have also been developed to improve the efficiency of dairy, beef, and pork production (KOPCHICK and CIOFFI 1991).

Coinciding with these technological developments, livestock industries have continued to pursue the largely untapped economic benefits available through traditional genetic selection for quantitative performance traits. As gene transfer and exogenous growth factor treatment become part of livestock production, optimization of these technologies in national genetic evaluation programs is vital. Simulation of dairy production in a system that includes exogenous treatments with growth hormone revealed scenarios in which traditional genetic evaluations may be significantly biased (BURNSIDE and MEYER 1988). The heritability of performance characteristics under the influence of a transgene or exogenous treatment, and the genetic correlation of performance with and without such influences are examples of parameters necessary to incorpo-

rate these practices into genetic evaluation programs. Unfortunately, estimates of these parameters have not been reported.

Changes in estimates of genetic parameters resulting from elevated growth hormone are also of interest from a basic quantitative genetics perspective, as they reflect changes in the expression of genes involved in the polygenic control of a trait. The effects of environmental influences on genetic variances have been widely studied in plants (ST. CLAIR and ADAMS 1991; WESSEL-BEAVER and SCOTT 1992; ROWE and BRINK 1993) and insects (GEBHARDT and STEARNS 1992; ASPI and HOIKKALA 1993), and the study of ontogenetic changes in genetic variation is well documented (ATCHLEY and RUTLEDGE 1980; CHEVERUD *et al.* 1983; ATCHLEY 1984, 1987), but the effects of transgene expression on components of quantitative variation are essentially unknown.

Thus, we conducted an investigation of the effect of elevated growth hormone level on components of phenotypic variation in growth traits using transgenic mice as a model. The specific objective of the present study was to determine if elevated growth hormone via a transgene affects the components of variation in growth. Hypotheses were that (1) significant additive variation in growth remains when growth hormone is elevated, (2) patterns of ontogenetic changes in variance components are affected by elevated growth hormone, and (3) the assortment of genes affecting growth traits is changed by elevated growth hormone. Implications for livestock genetic evaluation programs are considered.

Corresponding author: Archie C. Clutter, Department of Animal Science, Oklahoma State University, 206 ANSI, Stillwater, OK 74078-0425. E-mail: accosu@okway.okstate.edu

¹ Present address: University of Nebraska, Lincoln, NE 68504.

MATERIALS AND METHODS

Mice (*MG101*) possessing a sheep growth hormone transgene driven by a sheep 1 α -metallothionein promoter (*oMT1a-oGH*; SHANAHAN *et al.* 1989) exhibit dramatically increased growth and have proven to be an excellent model for study of the effects of increased growth hormone on a variety of metabolic and developmental processes (OBERBAUER *et al.* 1992; POMP *et al.* 1992). Growth hormone overexpression in *oMT1a-oGH* is almost fully inducible and retractable by the provision or removal of zinc in the drinking water (SHANAHAN *et al.* 1989). All other metallothionein-growth hormone constructs that have been reported result in elevated basal levels of growth hormone from neonate periods through adulthood, even in the absence of exogenous heavy metal induction. The high level of control of the *oMT1a-oGH* transgene, along with the ability to identify *oMT1a-oGH* transgenic mice at early preweaning ages (POMP and MURRAY 1991), enable controlled studies of the effects of growth hormone in mice from weaning through adult periods.

Mating design and animal husbandry: A variation of a classical mating design optimized for estimation of genetic parameters was adopted for the present study. Based on the capacity of the animal facility, the optimum number and size of families was determined for traits with moderate heritability using methods described by FALCONER (1989). Full- and half-sib families were produced by mating *MG101* males proven to be hemizygous for *oMT1a-oGH* with females from a four-strain composite (Harlan Sprague Dawley NIH $\times$ Harlan Sprague Dawley ICR $\times$ Charles River CF-1 $\times$ Charles River CFW) obtained from the University of Nebraska-Lincoln. Forty-three males were sampled from the *MG101* population at the University of California-Davis and each mated in the laboratory at Oklahoma State University to an average of 3.14 females. The females were from the early generations of a study of divergent selection for heat production (M. K. NIELSEN, personal communication) and were cross-classified by selection line (high, low, and control) when assigned to mating cages. Due to space constraints, the design was implemented in two consecutive replicates. Each male was placed in a mating cage with four females; after 2 weeks females were placed in individual litter cages. At birth, litters were standardized to 10 pups. Pups were toe-notched for identification at 10 days of age and characterized for presence of the transgene by PCR of toe-clip lysate (POMP and MURRAY 1991). The expectation for progeny of these matings was 1/2 hemizygous for the transgene (transgenic genotype) and 1/2 homozygous wild-type (control genotype). Pups were weaned at 21 days of age; females were randomly caged in groups of five, and males were caged by genotype in full-sib pairs. Ad libitum access to feed (Purina Laboratory Chow 5001) and water were provided. Beginning at weaning all mice received 25 mM zinc sulfate through the drinking water, an amount sufficient to stimulate expression of the transgene through the metallothionein-1a promoter. Room temperature was maintained at 23° and a 12L:12D photoperiod used.

Data collection and statistical analyses: Growth traits were measured on a total of 1237 male and female progeny. Mice were weighed weekly from weaning to 10 weeks of age. To characterize growth in the transgenic and wild-type progeny, the following logistic function (KOOBS 1986) was fitted to body weight data for each mouse:

$$y_t = a(1 + \tanh(b(t - d))) ,$$

where y_t is the weight at age t , a is one-half the upper asymptotic value of y , b is the growth rate relative to a , and d is the age at the inflection point.

Weights were regressed on the function for each animal using the NONLIN procedure of SAS (1988). As suggested

by KOOBS and GROSSMAN (1991), each animal was assigned a value of 0 for body weight at the time of conception ($y_t = 0$ at $t = -3$, assuming a 3-week gestation). Resulting parameter estimates for each animal were subjected to least-squares analysis with a model that included the effects of genotype (transgenic or wild type), sex and the genotype $\times$ sex interaction. Growth curves were derived from subclass means from the least-squares analysis, and subclass means for parameter estimates were contrasted with t -tests.

Components of variance for body weights at 3–10 weeks, and weight gains from 3–6 weeks and 6–10 weeks were estimated using an algorithm for multiple-trait derivative-free restricted maximum likelihood (MTDFREML; BOLDMAN and VAN VLECK 1991). Two sets of analyses were performed: (1) univariate analysis of each trait by genotype group and (2) bivariate analyses in which each weight or weight gain was treated as a different trait for transgenic and wild-type progeny (*e.g.*, 6-week weight for transgenics and for wild types defined as the two traits in a bivariate analysis). Each set of analyses provided estimates of the proportion of total (phenotypic) variance due to additive genetic effects (h^2), common litter effects (c^2), and residual environmental effects (e^2) in each genotypic group; the bivariate analyses also produced an estimate of the genetic correlation between transgenic and wild-type expression of each trait.

The model used for all traits in both the univariate and bivariate analyses included the fixed effects of replicate and sex, random additive genetic effects of animal, and random effects due to litter. In matrix notation, the bivariate model was

$$y = Xb + Z_1a + Z_2l + e,$$

where y is the vector of observations sorted by trait; b is the vector of fixed effects, replicate and sex; a is the vector of random additive genetic effects of animals; l is the vector of random litter effects; e is the vector of random residual effects; and X , Z_1 , and Z_2 are known incidence matrices. Additionally, $E(y) = Xb$, and the assumed variance/covariance structures for random effects were

$$V(a) = A^*G,$$

$$V(l) = I_l^*L, \text{ and}$$

$$V(e) = I_e^*R,$$

where G , L , and R are 2×2 variance/covariance matrices for additive genetic, common litter, and random residual effects, respectively, and $*$ denotes the direct matrix product. A is the numerator relationship matrix among all animals (progeny with records, and parents and ancestors without records), and I_l and I_e are identity matrices. For bivariate analyses in which animals only had a record for one or the other of the two traits, the off-diagonal elements of R were zero.

Some potential sources of bias should be noted. (1) Components of variance due to dominance and epistasis were assumed to be zero. MILLER *et al.* (1963) reported that these sources of variation were negligible for postweaning body weights in mice. (2) In general, maximum likelihood estimates are well-suited for unbalanced designs but can only assume values within the parameter space. Consequently, the estimates are easy to interpret but inherently biased. (3) Estimates of genetic parameters in the present analyses are based on records of progeny from an F_1 cross of diverse parental stock, thus are potentially biased due to linkage disequilibrium. However, if only additive effects are assumed, the disequilibrium effect can be plus or minus for each pair of loci and may tend toward zero when summed across all loci.

Because ontogenetic changes in variance components were of interest, and the magnitude of variances associated with these traits may be influenced by increases in body size, each

TABLE 1
Parameter estimates for logistic functions of growth in genotype $\times$ sex subclasses

Genotype	Sex	n	Parameter ^a		
			a	b	d
Transgenic	Male	302	19.61 $\pm$ 0.11	0.27 $\pm$.005	4.27 $\pm$ 0.03
	Female	247	18.76 $\pm$ 0.13	0.28 $\pm$.005	4.25 $\pm$ 0.03
Control	Male	395	14.53 $\pm$ 0.10	0.42 $\pm$.004	3.19 $\pm$ 0.03
	Female	293	11.83 $\pm$ 0.12	0.39 $\pm$.005	2.90 $\pm$ 0.03

^aa, one-half the upper asymptotic value of body weight (g); b, growth rate relative to a; d, age at the inflection point (week).

trait was analyzed as both a raw measurement and after log transformation (logarithms to base 10) in an attempt to uncouple variance and mean (ATCHLEY 1984). In all analyses, relationships among animals with records through the half- and full-sib mating design, and those among sires and among dams through ancestors traced back two generations were accounted for in the relationship matrix.

MTDFREML is an iterative procedure and convergence was assumed at the round of iteration at which the variance of log likelihood evaluations was 1×10^{-9} or less. At least three restarts using estimates at previous convergence were performed for each analysis to help ensure that a global rather than a local maximum of the likelihood function had been reached.

In general, algorithms for derivative-free REML do not provide estimates of sampling errors as a byproduct, and alternative approximations of errors were not available in the MTDFREML program package. Methods that fit a polynomial function to the likelihood surface have been developed to approximate standard errors and confidence intervals for parameter estimates from derivative-free REML (MEYER and HILL 1992), but the procedures can be computationally demanding and may produce unacceptable results for specific models and unbalanced data.

As an alternative, we chose to use information available with the MTDFREML programs to evaluate some relatively simple hypotheses with likelihood ratio tests (KENDALL and STUART 1979; SHAW 1987, 1991). These tests are intuitively straightforward, the test statistic based on the difference between the value of the log likelihood under the conditions of the null hypothesis and the (unconditional) maximum value of the log likelihood, and are possible without characterization of the likelihood surface. Results from univariate analyses were used to determine the significance of additive genetic effects for each trait by comparing the log likelihood for a model in which the additive genetic variance (V_a) was constrained to zero (L_0) to the log likelihood for the unconstrained model ($L_{\max}$). The value of $-2(L_0 - L_{\max})$ is asymptotically distributed as χ^2 with 1 degree of freedom (KENDALL and STUART 1979). The common litter effect was expected to capture one-half of the additive genetic variance in the constrained model. In that respect, the result was considered a conservative test of $H_0: V_a = 0$. The hypothesis that the genetic correlation (r_a) = 1.0 was tested for each of the bivariate analyses by comparing the log likelihood for a model in which r_a was constrained to ~ 1.0 (0.99) to the log likelihood from the unconstrained model. These tests addressed relevant hypotheses in the study and provided an indication of the precision with which we were able to estimate genetic parameters.

RESULTS AND DISCUSSION

Least-squares means for estimates of curve parameters are in Table 1 and the logistic growth curves for the

transgenic and wild-type (control) groups are plotted by sex in Figure 1. There was a genotype $\times$ sex interaction ($P < 0.01$) for each of the estimated parameters. Transgenics exhibited faster and more prolonged growth ($P < 0.01$), but the effects were more pronounced in females than in males relative to controls. As a result, typical gender differences in growth were reduced by the transgene. The period of most rapid growth ranged from ~ 2.9 to 3.2 weeks of age in the controls, but was 4.25 weeks in the transgenics. At 10 weeks of age, transgenic males and females were 26% (36.4 vs. 28.8 g) and 49% (35.0 vs. 23.5 g) heavier, respectively, than their wild-type contemporaries ($P < 0.01$). Control mice had stopped growing by week 10, but transgenics only approached their predicted asymptotic value of ~ 38 g.

The overall effect of the transgene in the present study, as well as the interaction of the transgene with gender, is similar to results from a previous report of *MG101* progeny from a different maternal genetic background (POMP *et al.* 1992). In studies of mice with human and bovine growth hormone transgenes (KOOPS and GROSSMAN 1991; EISEN *et al.* 1993), transgene $\times$ sex interactions were also reported. But in the latter study (EISEN *et al.* 1993), the transgene had a greater effect in males than in females.

Estimates of phenotypic variances in unadjusted and log-adjusted body weights from 3 to 10 weeks of age are presented for the control group in Figure 2 to show the effects of log transformation. The scales of the y axes are, thus, in different units, but are aligned for comparison of the relative ontogenetic patterns. Variances from unadjusted data increased from 3 to 4 weeks of age, decreased slightly from 4 to 6 weeks, and increased linearly thereafter. For log-adjusted data, the variance increased from 3 to 4 weeks, decreased to 6 weeks and then remained relatively constant. The pattern of change for log-adjusted data is similar to reports of various other mouse populations when data were log-adjusted (ATCHLEY 1984) and indicates that much of the effect of scaling on the variance has been alleviated by the transformation. Therefore, the remainder of the present report will include only results from log-transformed analyses.

Estimated components of variance and the proportion of phenotypic variation explained by each (h^2 , c^2 ,

FIGURE 1.—Logistic growth curves of the transgenic (TG) and wild-type (CL) males and females. See Table 1 for growth curve parameters.

and e^2) from the univariate analyses are presented in Table 2; estimates of the same components from the bivariate analyses are presented in Table 3. Estimates of corresponding variance components and patterns in changes of components with ontogeny were generally similar for univariate and bivariate analyses. The greatest difference was for additive genetic variance and corresponding h^2 at 3 weeks of age. Figures 3 and 4 depict ontogenetic changes in estimates from bivariate analyses of weights through 10 weeks of age.

Additive genetic variances were significant ($P < 0.05$) or approached significance ($P < 0.10$) for body weights at all ages in the control progeny, except for week 4 and week 10. Corresponding estimates of heritabilities were similar to those from literature reports for pre-

weaning and postweaning body weights (MALIK 1984). The estimated genetic variances for gains from 3 to 6 and 6 to 10 weeks in the control group were not different from zero, but the heritability for 3 to 6 week gain from the bivariate analysis (0.23) was within the range of literature reports for the trait (MALIK 1984; EISEN and PRASETYO 1988). Estimates of additive genetic variances for body weights in the transgenic group were significant ($P < 0.05$) or tended to be significant ($P < 0.10$) at all ages except 5 and 9 weeks, and for both measurements of gain.

As previously discussed, the constrained univariate model applied in the likelihood ratio tests resulted in what was considered a conservative test of $H_0: V_a = 0$, and measurement of the power of likelihood ratio tests

FIGURE 2.—Estimates of phenotypic variances in unadjusted (left) and log-adjusted (right) body weights for the control group. The scales of the y axes are in different units but are aligned for comparison.

TABLE 2

Estimates of variance components and proportions of total phenotypic variance from univariate analyses by genotype

Trait	Control						Transgenic					
	σ_a^2	σ_c^2	σ_e^2	h^2	c^2	e^2	σ_a^2	σ_c^2	σ_e^2	h^2	c^2	e^2
3-wk weight	7.68**	15.52	5.19	0.27	0.55	0.18	6.90**	10.97	4.13	0.31	0.50	0.19
4-wk weight	2.93	18.15	16.69	0.08	0.48	0.44	8.51*	8.40	13.95	0.28	0.27	0.45
5-wk weight	5.45 [†]	7.52	8.92	0.25	0.34	0.41	2.42	5.61	15.71	0.10	0.24	0.66
6-wk weight	6.52**	2.79	5.43	0.44	0.19	0.37	3.37 [†]	3.60	10.30	0.20	0.21	0.60
7-wk weight	5.16*	3.43	5.54	0.37	0.24	0.39	4.59*	3.79	10.16	0.26	0.16	0.58
8-wk weight	5.95*	3.45	5.31	0.40	0.23	0.36	5.74*	2.89	11.37	0.29	0.14	0.57
9-wk weight	4.47*	3.49	6.86	0.30	0.24	0.46	3.87	3.55	13.74	0.18	0.17	0.65
10-wk weight	2.78	4.07	8.00	0.19	0.27	0.54	7.34*	3.10	12.67	0.32	0.13	0.55
Gain 3–6	6.39	15.33	31.09	0.12	0.29	0.59	31.42**	17.27	27.76	0.41	0.23	0.36
Gain 6–10	0.00	50.94	392.56	0.00	0.11	0.89	99.76*	30.47	148.70	0.36	0.11	0.53

 σ_a^2 , additive genetic; σ_c^2 , common litter; σ_e^2 , residual; h^2 , heritability; c^2 , common litter; e^2 , residual.** $P < 0.01$; $H_0: \sigma_a^2 = 0$. * $P < 0.05$; $H_0: \sigma_a^2 = 0$. [†] $P < 0.10$; $H_0: \sigma_a^2 = 0$.

through simulation has shown them to be generally conservative (SHAW 1987). Conversely, the error rates presented here may be somewhat underestimated due to the correlation among sequential weights. Given these considerations, all but three of the estimates of additive variance in the transgenic group were significant at $\alpha = 0.05$, and for 3–6-week gain the estimate was significant at a relatively stringent criterion ($\alpha = 0.01$). To our knowledge these are the first reported estimates of genetic variances and heritabilities in transgenic animals. For these traits of body size and growth, a significant amount of genetic variation existed in the presence of prolonged elevated growth hormone via transgene expression.

Differences in estimates of additive genetic variance and in the ontogenetic patterns of change in genetic variances for the control and transgenic groups (Figure 3) were apparently within the range of sampling error, except for perhaps the pattern from 3 to 4 weeks of

age. The greatest amount of genetic variance was at 3 weeks in the control group and at 4 weeks in transgenics, corresponding with their respective periods of greatest growth. Estimates of genetic variance in the control group declined greatly from 3 to 4 weeks, then steadily through 10 weeks, while estimates for transgenics increased from 3 to 4 weeks and then tended to decline.

ATCHLEY (1984) summarized several studies of the ontogeny of genetic parameters in nontransgenic mice and rats. He concluded that both additive genetic and phenotypic variances increased as growth accelerated, peaked at approximately the inflection point or period of maximum growth, then declined as the growth curve approached the asymptote. If the patterns in genetic variances for the control and transgenic groups were in fact different from 3 to 4 weeks, the difference may have been related to the later inflection point in the growth curves of the transgenic animals (Table 1). How-

TABLE 3

Estimates of variances and covariances from bivariate analyses and corresponding proportions of phenotypic variance and correlations

Trait	Control						Transgenic						Covariability			
	σ_a^2	σ_c^2	σ_e^2	h^2	c^2	e^2	σ_a^2	σ_c^2	σ_e^2	h^2	c^2	e^2	$\sigma_{a_{wt}}$	r_a	$\sigma_{c_{wt}}$	r_c
3-wk weight	16.49	14.14	0.66	0.53	0.45	0.02	7.25	11.33	3.87	0.32	0.50	0.17	10.91	1.00	12.48	0.99
4-wk weight	8.98	16.50	13.53	0.23	0.42	0.35	12.43	8.07	11.67	0.39	0.25	0.36	10.19	0.96	9.93	0.86
5-wk weight	7.65	6.39	7.85	0.35	0.29	0.36	6.58	4.49	13.36	0.27	0.18	0.55	7.10	1.00	4.73	0.88
6-wk weight	7.36	2.44	5.03	0.50	0.16	0.34	4.79	3.13	9.55	0.27	0.18	0.55	4.56	0.77	1.95	0.70
7-wk weight	6.38	3.01	4.92	0.45	0.21	0.34	5.29	2.56	9.80	0.30	0.15	0.56	3.79	0.65	1.70	0.61
8-wk weight	6.98	3.10	4.79	0.47	0.21	0.32	5.87	2.78	11.32	0.29	0.14	0.57	2.97	0.46 [†]	1.63	0.56
9-wk weight	4.85	3.36	6.67	0.33	0.23	0.45	4.04	3.49	13.65	0.19	0.16	0.64	2.03	0.46	1.67	0.49
10-wk weight	3.96	3.65	7.40	0.26	0.24	0.49	7.52	3.04	12.58	0.33	0.13	0.54	3.58	0.66	1.10	0.33
Gain 3–6	12.09	12.60	28.31	0.23	0.24	0.53	29.97	17.71	28.44	0.39	0.23	0.37	19.03	1.00	9.56	0.64
Gain 6–10	5.40	49.39	389.79	0.01	0.11	0.88	105.02	28.53	145.94	0.38	0.10	0.52	23.81	1.00	5.39	0.14

σ_a^2 , additive genetic; σ_c^2 , common litter; σ_e^2 , residual; $\sigma_{a_{wt}}$, additive covariance between wild type (control) and transgenic; $\sigma_{c_{wt}}$, common litter covariance between wild type (control) and transgenic; h^2 , heritability; c^2 , common litter; e^2 , residual; r_a , genetic correlation; r_c , common litter correlation.

[†] $P < 0.10$; $H_0: r_a = 1.0$.

FIGURE 3.—Estimates of components of variance for log-adjusted body weights in the wild-type (control) and transgenic groups.

ever, the patterns in phenotypic variances over the same age period were similar for the groups.

The corresponding ontogenetic changes in additive genetic and phenotypic variances, as summarized by ATCHLEY (1984), result in a relatively age-constant heritability for body weight. Fluctuations in heritabilities for each group in the present study (Figure 4) are likely due to sampling and do not dispute the hypothesis of a constant heritability, nor is there clear evidence of an average difference in heritabilities between the groups. There was, however, a tendency for the control group to have a greater heritability for body weights from 5

weeks through 9 weeks than transgenics. This result may be due to larger, and apparently increasing, residual and phenotypic variances in the transgenic group.

Changes with age in the variance due to common litter effects were generally similar in the control and transgenic groups (Figure 3). The variance in the control group was nearly constant from 3 to 4 weeks of age, while in transgenics the variance began to decline over the same period, but there was a general decline in both groups following weaning at 3 weeks. This variance component reflects differences in maternal influences between litters, and the pattern of decline agrees with

FIGURE 4.—Proportion of total phenotypic variance in log-adjusted body weights of wild-type (control) and transgenic groups due to additive genetic (h^2), common litter (c^2) and residual environmental (e^2) effects.

FIGURE 5.—Estimated additive genetic and common litter effect correlations between wild-type and transgenic log-adjusted body weights at each age.

several reports in the literature (MOORE *et al.* 1970; ATCHLEY and RUTLEDGE 1980; CHEVERUD *et al.* 1983; ATCHLEY 1984; COWLEY *et al.* 1989). However, COWLEY *et al.* (1989) also reported that maternal uterine environment continued to influence body weight through 9 weeks of age. It is important to note in the context of the present study that maternal influences on growth were a significant source of variation among transgenic animals and accounted for >10% of phenotypic variance as late as 10 weeks (Figure 4).

Estimates of the covariances between additive genetic effects and between common litter effects on each trait in transgenics and controls, along with corresponding correlations, are presented in Table 3. The correlations for body weights are also plotted in Figure 5. Both additive genetic and common litter correlations displayed a pattern of decline with ontogeny from estimates of (approximately) 1.0 at 3 weeks of age. The linear regressions of each correlation on week of age were -0.08 ($P < 0.01$) and -0.09 ($P < 0.01$) for additive genetic and common litter, respectively. However, among the genetic correlations, only the estimate at 8 weeks of age tended to be significantly different from 1.0 ($P < 0.10$). Estimates of the genetic correlation between expression of gains in transgenics and controls were ~ 1.0 .

The additive genetic correlation between body weight at a given age in control and transgenic animals measures the degree to which the same genes (or linked genes) affect expression of the trait in the two groups. Similarly, the common litter correlation measures the degree to which the same maternal factors influence body weight at a given age in transgenic and nontransgenic animals. The patterns of decline in both these correlations suggest that as the transgene is expressed over time, a different set of genes and of factors associated with maternal environment may begin to influence body weight.

Quantitative geneticists have long considered changes in additive genetic variance with ontogeny to be due to

the switching on and off, and temporal expression, of the various genes involved in developmental processes (ATCHLEY and RUTLEDGE 1980; ATCHLEY 1984). The increase in genetic variance associated with the period of most rapid growth, for example, has been attributed to expression of a greater number of genes (ATCHLEY and RUTLEDGE 1980). Changes in gene action may also occur with changes in the physiological environment. ROTHCHILD *et al.* (1996) report a major effect on litter size in the pig associated with the estrogen receptor gene that is additive in the first parity but dominant in later parities. Recent applications of a saturated marker map of the mouse genome in segregating populations has resulted in identification of specific chromosomal regions associated with variation in body weight at various stages of development (D. POMP, unpublished data). A similar strategy using a segregating population with and without the *oMT1a-oGH* transgene would allow identification of unique loci and changes in gene action that contribute to variation in body weight at different ages in an environment of elevated growth hormone.

Results from the present study reveal several points with potential implications for scenarios of genetic improvement. The *oMT1a-oGH* transgene has a dramatic effect on growth rate and body size through physiological pathways (CHOW *et al.* 1994) that are likely large contributors to normal genetic variation (BLAIR *et al.* 1989; CLUTTER *et al.* 1995). Yet, a significant amount of additive genetic variation remains available for exploitation by selection in the transgenic population. Variation in growth and body weight due to maternal effects was of similar importance in an environment of elevated growth hormone in the transgenic population and in controls. Last, a partially different array of genes in transgenic and nontransgenic animals may determine the additive variation associated with some traits. Consequently, methods of genetic evaluation that consider one characteristic to be different traits in the presence or absence of exogenous treatment

(BURNSIDE and MEYER 1988), or in transgenics and non-transgenics may be necessary.

Precise estimation of genetic parameters in experimental populations is difficult (KOOTS and GIBSON 1994), and results of the present study provide only an initial and general picture of genetic variation in transgenic animals. The recent application of growth hormone treatments in dairy cattle management will result in data bases suited for the study of the effects of elevated growth hormone on genetic variances and covariances for dairy traits. Further study of various constructs in transgenic mouse populations with the aid of molecular tools should provide a clearer picture of the specific interactions of transgenes with quantitative variation. In summary, results from the present study indicate that overexpression of an important peptide such as growth hormone may alter the genetic control of growth, but that significant additive genetic variation remains.

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