A GENETIC ANALYSIS OF TARGETED GROWTH IN MICE

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Manuscript received June 2, 1983
Revised copy accepted January 16, 1984

ABSTRACT

Effects of normal growth regulation on components of phenotypic variance and covariance of body weight were examined in a cross-fostering study of growth between 2 and 10 wk of age in ICR randombred mice. Different early growth rates caused genetic, postnatal maternal and residual environmental variances to increase, but these variances were subsequently reduced by negative autocorrelation between early and later growth. Postnatal maternal variance continued to increase for about 1 wk after weaning but then decreased substantially. Genetic variance caused by preweaning growth followed a pattern of increase and decrease very similar to that of postnatal maternal variance, but this pattern was masked by new genetic variance. Normal growth regulation affects the magnitudes of genetic variances and serial autocorrelations. The timing of these changes suggests that regulation of cell numbers reduces variance near the end of exponential growth, but this may be obscured by subsequent increase in cell size. In contrast with earlier studies, we find that targeted growth reduces both genetically and environmentally determined differences among early growth trajectories. Final size may be determined by an antagonistic balance between early growth rate and age at initiation of puberty.

NORMAL growth in mammals follows many routes to a common destination. Although temporarily scattered by differing circumstances, the growth curves of individual members of a cohort eventually converge on a restricted range of adult phenotypes (VON BERTALANFFY 1960; MONTEIRO and FALCONER 1966; TANNER 1963). Prolonged environmental stress can cause permanent damage, but the effects of temporary starvation or illness are often corrected by "catch-up growth," which rapidly returns the individual to a normal growth trajectory (WILSON and OSBOURN 1960; TANNER 1963; WINICK, FISH and ROSSO 1968). Similarly, quantitative genetic studies of body-weight growth in mammals have shown that differences in early growth rates caused by a variety of environmental factors are at least partly compensated by later growth (MONTEIRO and FALCONER 1966; DICKINSON 1960; MOORE, EISEN and ULBERG 1970).

This tendency of growth trajectories to converge on a reduced range of phenotypes has been labeled "targeted growth" (TANNER 1963), "compensatory growth" (MONTEIRO and FALCONER 1966) and "equifinality of growth" (VON BERTALANFFY 1960). In this paper we refer to divergence of growth trajectories in a cohort as "divergent growth," and their subsequent convergence as "convergent growth" or "compensatory growth."

We present evidence that compensation occurs not only in environmentally induced variance but in genetic as well. If genetic variances or covariances of morphological traits change during growth, predicted direct and correlated responses of the traits to selection are also likely to change (FALCONER 1981; LANDE 1979). Values of a trait at different times during growth may be viewed as a series of traits, connected during development and evolution by serial genetic and environmental autocorrelation. Because this connection is one route by which developmental and evolutionary change may interact, it is an important aspect both of short-term artificial selection schemes and of attempts to relate developmental and phylogenetic change (*e.g.*, TURNER and YOUNG 1969; ALBERCH *et al.* 1979).

In this study we present estimates of age-specific genetic and environmental parameters for body weight during postnatal growth in a large sample of randombred mice. We discuss theoretical and empirical effects of targeted growth on these parameters and implications of our results for genetic models of growth regulation.

MATERIALS AND METHODS

Randombred ICR mice obtained from Sprague-Dawley were randomly pair mated, and subsequent litters were standardized at birth to eight pups, usually four of each sex. Four pups from each standardized litter, chosen randomly except that two of each sex were taken where possible, were exchanged with similarly chosen offspring from an unrelated mother. This cross-fostering pair forms the basic unit of the experiment. All offspring in a cross-fostering pair were born on the same day. Pups were forcibly weaned at 3 wk of age and maintained in single-sex cages of less than five mice each, with unlimited food and water. Four mice from each liter were weighed each week on their birth date at ages 2 through 10 wk. The experiment was conducted in two batches at different times in the same laboratory and with the same husbandry and measurement techniques. Results reported here are based upon a total of 345 cross-fostering pairs including 2693 offspring: 1346 male and 1347 female.

After transformation to natural logarithms, body weights were analyzed by analysis of variance, and resulting variance components were equated with genetic expectations following RUTLEDGE *et al.* (1972). Data from each cross-fostering pair correspond to a two-by-two table in which the levels of the two factors are the two mothers, with one factor assigning offspring by genetic mother, the other by nursing mother. Each complete pair yielded variation corresponding to 1 d.f. for the effect of genetic mother and 1 d.f. for the effect of nurse, plus residual variance including any mother-nurse interaction and variance among full sibs with a common nurse.

Variance components were estimated by the VARCOMP general linear model procedure described by BARR *et al.* (1979). To reduce size of the design matrix, each of the two batches was processed as three groups of about the same number of pairs, and variance components from these were averaged, weighted by number of mice per group. The weighted average of the two resulting components was used to estimate genetic parameters. Additive genetic variance was estimated as twice the variance component for genetic mother, postnatal maternal variance was equated with the component for postnatal mother and residual environmental variance was estimated as the residual after subtracting the component for genetic mother from the pooled interaction and residual within-cell components. Estimates of additive genetic and residual environmental variance each include half of any dominance variance, and the postnatal maternal estimate includes any variance due to differences between preweaning cages, as these are completely confounded with nursing mothers. The contribution of dominance and other nonadditive sources to variance of body weight in mice is believed to be small (MONTEIRO and FALCONER 1966; MILLER, LEGATES and COCKERHAM 1963), although HERBERT, KIDWELL and CHASE (1979) estimated that nonadditive components accounted for as much as 10% of total variance in body weight. Differences between cages should have little effect, as uniform cages and husbandry techniques were used. Prenatal maternal effects are confounded with our genetic

estimate, but evidence that these effects are negligible is presented. Standard errors of variance components were estimated as outlined by KEMPTHORNE (1969, pp. 245–246), using unbiased estimates of variances of mean squares.

To obtain components of phenotypic covariance between weights at two ages, corresponding variance estimates for each of the ages were subtracted from that for their sum, and the residual was divided by 2. In addition to body weights, weekly weight gains were analyzed as the differences between natural logs of successive weights.

Many of these analyses were also performed on untransformed data, and results for log-transformed and untransformed data are compared.

RESULTS

Growth: Figure 1 shows untransformed mean weights through time for each sex. After an early exponential growth phase, the curves pass through inflection points at 22 and 20 days for males and females, respectively, as estimated from the mean age at inflection for Gompertz growth curves (LAIRD, TYLER and

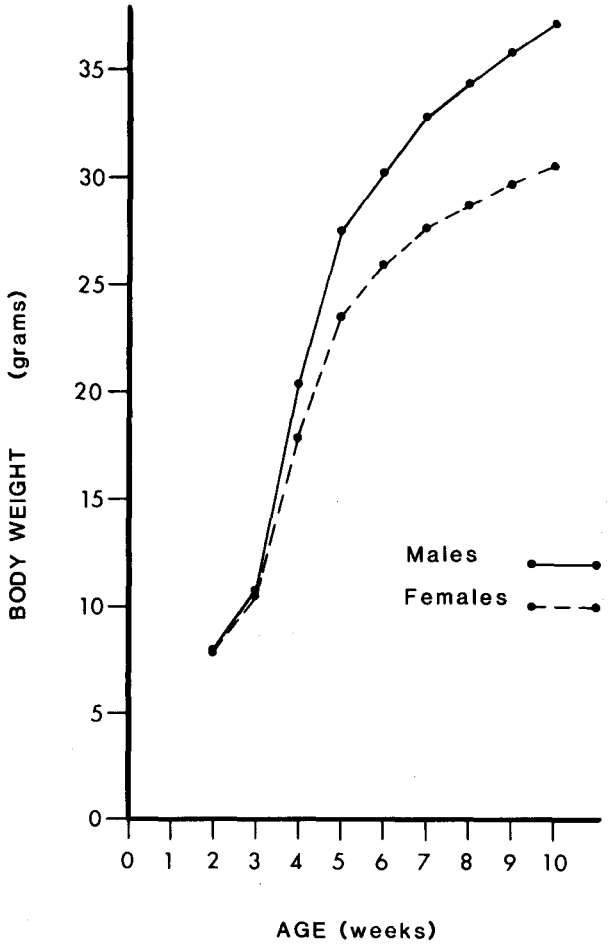

FIGURE 1.—Mean body weight in grams as a function of age in weeks. Means are for 1346 male and 1347 female mice.

TABLE 1

Components of phenotypic variance of log-transformed mouse weights

Age (wk)	$V_A \pm$ SE	$V_M \pm$ SE	$V_E \pm$ SE	$V_P \pm$ SE	Heritability (%)
			Males		
2	436 ± 90	1360 ± 136	262 ± 59	2057 ± 149	21
3	808 ± 171	1540 ± 167	607 ± 116	2955 ± 203	27
4	558 ± 126	1066 ± 124	448 ± 86	2072 ± 151	27
5	200 ± 57	283 ± 42	264 ± 41	747 ± 58	27
6	137 ± 41	132 ± 25	206 ± 30	475 ± 39	29
7	144 ± 39	94 ± 22	194 ± 29	432 ± 36	33
8	130 ± 40	89 ± 22	216 ± 30	434 ± 37	30
9	127 ± 48	53 ± 24	292 ± 37	471 ± 44	27
10	165 ± 54	31 ± 25	302 ± 41	498 ± 48	33
			Females		
2	541 ± 104	1478 ± 144	242 ± 67	2261 ± 159	24
3	975 ± 174	1490 ± 155	379 ± 111	2844 ± 190	34
4	673 ± 118	821 ± 95	259 ± 76	1753 ± 122	38
5	248 ± 61	303 ± 43	255 ± 43	806 ± 61	31
6	207 ± 51	163 ± 29	218 ± 36	587 ± 47	35
7	261 ± 53	155 ± 28	191 ± 36	607 ± 46	43
8	257 ± 58	125 ± 29	242 ± 41	624 ± 50	41
9	314 ± 67	161 ± 34	260 ± 47	736 ± 58	43
10	272 ± 67	184 ± 37	309 ± 48	765 ± 61	36

V_A = Additive genetic variance; V_M = postnatal maternal variance; V_E = environmental variance; V_P = phenotypic variance. Variances in units of (log$_e$ grams)^2 have been multiplied by 10^5.

BARTON 1965) fitted to data for each mouse. By 6 wk of age, growth has begun to level off in a linear phase that persists to the end of the experiment. LAIRD, TYLER and BARTON (1965) have suggested that growth consists of exponential and linear components, both of which are active throughout postnatal growth but with the linear only becoming apparent well beyond the inflection point of the curve. Here we shall use "linear phase" to designate only the top of the curve (after about 6 or 7 wk) where exponential models fit poorly. The curves shown here are typical of those for mice, rats and other mammals (MONTEIRO and FALCONER 1966; RUTLEDGE *et al.* 1972; EISEN 1975; LAIRD 1966).

Variance of body weight during growth: Total phenotypic variance of log-transformed body weight and its genetic, postnatal maternal and residual environmental components all show similar patterns of change with growth (Table 1, Figure 2). Variance increases or is initially high until about 3 wk of age; it then decreases until about 6 wk, after which additional increase may occur. This pattern is most pronounced in the postnatal maternal component. For environmental variance, males show a higher initial increase than females, but also a correspondingly larger decrease, so that environmental variance in the two sexes is approximately equal from 5 wk on. Heritability is always higher in females than in males. For all components of variance, early heterogeneity in exponential

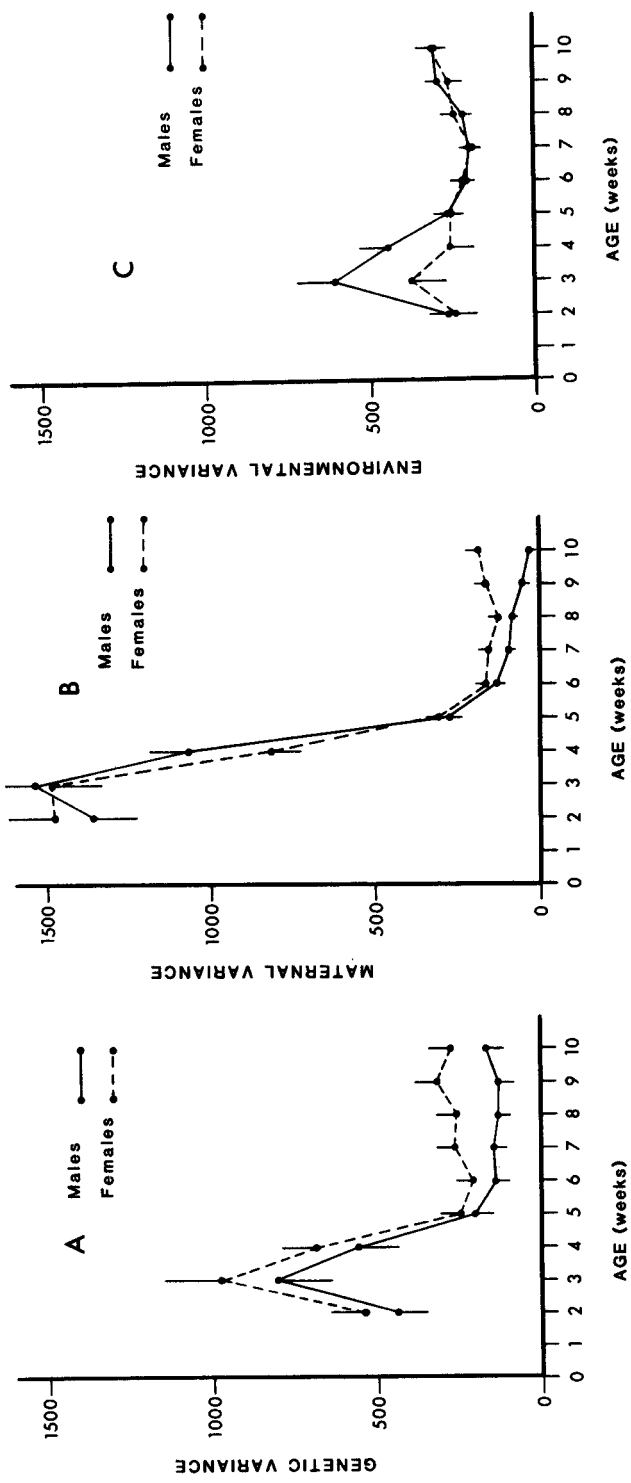

FIGURE 2.—Components of phenotypic variance of log-transformed body weight as a function of age. Vertical bars represent 1 SE. A, Additive genetic variance; B, postnatal maternal variance; C, residual environmental variance.

TABLE 2

Components of phenotypic variance of gains in log-transformed weight

Age (wk)	$V_A \pm$ SE	$V_M \pm$ SE	$V_E \pm$ SE	$V_P \pm$ SE	Heritability (%)
		Males			
2–3	200 ± 63	265 ± 44	344 ± 47	809 ± 64	25
3–4	38 ± 47	106 ± 30	374 ± 40	518 ± 50	7
4–5	187 ± 46	240 ± 34	189 ± 32	616 ± 47	30
5–6	55 ± 18	33 ± 9	86 ± 13	174 ± 16	31
6–7	10 ± 9	−5 ± 4	72 ± 8	78 ± 9	14
7–8	−17 ± 8	−7 ± 4	83 ± 7	59 ± 8	0
8–9	2 ± 13	−14 ± 6	102 ± 11	90 ± 13	2
9–10	8 ± 15	−17 ± 7	118 ± 13	109 ± 15	7
		Females			
2–3	84 ± 49	313 ± 43	328 ± 39	725 ± 58	12
3–4	105 ± 49	193 ± 34	316 ± 38	614 ± 51	17
4–5	108 ± 38	110 ± 23	217 ± 29	434 ± 37	25
5–6	−1 ± 22	4 ± 18	189 ± 19	192 ± 22	0
6–7	19 ± 17	−1 ± 9	137 ± 14	156 ± 17	12
7–8	−2 ± 20	2 ± 11	185 ± 18	186 ± 21	0
8–9	26 ± 30	−4 ± 15	247 ± 25	269 ± 29	10
9–10	18 ± 38	−5 ± 19	323 ± 33	336 ± 38	5

V_A = additive genetic variance; V_M = postnatal maternal variance; V_E = environmental variance; V_P = phenotypic variance. Variances in units of (log$_e$ grams)^2 have been multiplied by 10^5. Where variance estimates were negative the estimated value is shown in the table, although the true value must be non-negative.

growth rates causes growth trajectories to diverge, but the trajectories later converge near the end of exponential growth.

Variance of weight gain: Components of variance for gain in log-transformed weight are shown in Table 2.

Total phenotypic variance of weight gain is highest between 2 and 3 wk, decreases to a low point at near 7 wk and increases slightly beyond this. Early heterogeneity in growth rates decreases to uniformity near the transition from exponential to linear growth, followed by some subsequent divergence.

Genetic variance of weight gain is highest during the first 5 wk, corresponding to the peak and decrease in genetic variance of weight. In males this lasts longer than in females, but in both sexes heritability of weight gain for log-transformed data is low or zero after 6 or 7 wk.

Postnatal maternal variance in weight gain is also highest between 2 and 5 wk, when maternal variance in weight peaks and drops. After 6 wk there is little or no maternal variance in weight gain in either sex. From a high of 30 or 40% during exponential growth, the maternal component of gain dwindles to nothing in the linear phase.

Environmental variance of weight gain is highest from 2 to 4 wk, declines to a low at 6 to 7 wk and then increases steadily. Males have a higher value for the first 2 wk but afterward always have less environmental variance in weight gain

TABLE 3

Correlations between log-transformed mouse weights at different ages

	Age (wk)								
Age (wk)	2	3	4	5	6	7	8	9	10
					Phenotypic				
2		85	86	79	71	64	59	56	53
3	86		91	81	70	63	58	55	51
4	85	89		89	79	70	65	60	56
5	79	80	89		88	82	78	72	69
6	73	74	82	87		92	88	83	78
7	66	68	77	82	87		93	88	85
8	62	61	71	78	85	85		90	88
9	63	63	71	76	81	84	80		89
10	60	59	67	72	79	82	83	78	
					Genetic				
2		88	86	74	64	59	47	48	43
3	99		99	77	48	50	36	36	28
4	93	95		85	68	58	54	50	37
5	85	81	100		85	75	76	66	57
6	76	71	97	101		96	97	87	80
7	71	63	85	88	97		106	99	87
8	56	57	78	85	97	100		99	97
9	66	59	78	79	90	90	96		98
10	57	55	71	76	90	98	92	97	
					Environmental				
2		66	56	59	56	46	50	36	48
3	48		65	62	69	49	54	41	50
4	32	51		76	74	61	57	45	58
5	37	51	58		82	77	68	64	69
6	42	49	43	60		82	77	73	72
7	22	40	40	63	67		80	75	81
8	31	29	37	58	62	58		81	79
9	10	23	28	51	60	65	51		80
10	21	27	37	50	52	54	66	43	

All correlations have been multiplied by 100. In each matrix, correlations for males are given above the main diagonal, females below. Estimated correlations greater than 1 result from sampling variance in estimates of variance and covariance components.

than females. Between 2 and 3 wk, about 40 to 45% of variance in weight gain is environmentally induced. Between 7 and 10 wk, virtually all variation in relative gain is environmental.

Correlations between age-specific weights: Correlations between log-transformed age-specific weights (Table 3) are all positive. Phenotypic and genetic correlations are highest between chronologically adjacent weights. Environmental correlations are generally weaker than genetic or postnatal maternal. Postnatal maternal correlations (not shown in Table 3) are near unity, except the correlation between 2- and 3-wk weights, which is lower, near 0.9. This is because postnatal family

TABLE 4

Correlations between gains in log-transformed mouse weight

	Age (wk)							
Age (wk)	2–3	3–4	4–5	5–6	6–7	7–8	8–9	9–10
				Phenotypic				
2–3		−57	−37	−25	−10	−06	0	−03
3–4	−54		14	19	0	08	−08	−02
4–5	−26	18		28	30	11	04	07
5–6	−08	08	09		0	06	03	0
6–7	−01	07	05	−23		−23	05	08
7–8	−09	07	12	06	−47		−28	06
8–9	04	−08	−11	−05	12	−53		−44
9–10	−05	03	04	07	−02	13	−59	
				Genetic				
2–3		−54	−77	−84	47	–	0	−37
3–4	−51		98	109	−169	–	−137	−43
4–5	−131	102		39	21	–	−45	50
5–6	–	–	–		48	–	37	30
6–7	−31	−15	02	–		–	69	−55
7–8	–	–	–	–	–		–	–
8–9	−43	−20	−52	–	−30	–		01
9–10	19	−22	76	–	96	–	0	
				Environmental				
2–3		−54	−22	12	−32	09	03	04
3–4	−47		−35	−18	20	−19	05	03
4–5	−05	−41		−29	23	−05	20	−22
5–6	−08	−11	−33		−30	10	02	−15
6–7	07	10	06	−49		−36	−01	18
7–8	−20	09	01	01	−46		−31	−18
8–9	12	−01	03	05	11	−63		−49
9–10	−03	03	−08	−06	−03	23	−67	

All correlations have been multiplied by 100. In each matrix, correlations for males are given above main diagonal, females below. Dashes indicate correlation undefined because of nonpositive variance estimate. Estimated correlations less than −1 or greater than 1 result from sampling variance in estimates of variance and covariance components.

means are still diverging between 2 and 3 wk. After 3 wk, however, the pattern of variation among postnatal families is essentially constant, although the relative magnitude of variation is reduced by compensatory or convergent growth.

Correlations between weekly gains in weight: Correlations between gains in log-transformed weight are shown in Table 4.

Phenotypic correlations between weight gains are nearly all zero or slightly negative. Exceptions to this occur during the first 5 wk in females and the first 6 wk in males, because of divergent growth through age 3 wk, followed by convergent growth from 3 to nearly 6 wk. The pattern spans slightly more time in males than females because of the larger environmental variance generated by 3 wk and longer convergence in the genetic component. There are also

negative correlations between sequential gains in the 6- to 10-wk period, probably partly due to artifactual negative correlations in the environmental component (see following discussion).

Genetic correlations between weekly gains are similar to phenotypic correlations. Gain from 2 to 3 wk is negatively correlated with most other gains, and there are positive correlations between 3–4 and 4–5 wk in females and between these and 5–6 wk in males, again reflecting the periods of divergent and convergent growth.

Postnatal maternal correlations between weekly gains, like other components, show the contrast between 2- to 3-wk gain and subsequent gains. (These correlations are not shown in the table.)

Environmental correlations between weekly weight gains are largely negative for 2–3 wk *vs.* subsequent gains, especially in males. With the exception of those between chronologically adjacent gains, other correlations are small in absolute value and may be estimating a true correlation near zero. Negative correlations between sequential gains after about 5 wk of age are probably partly an artifact of measurement variance, including daily variation in body weight. Because final weight for one gain estimate is initial weight for the next, random variation in this common weight estimate will induce a negative correlation between the two gain estimates. If A, B and C represent sequential weekly weight estimates,

$$\text{cov}(B\text{-}A,\ C\text{-}B) = \text{cov}(B,\ C) + \text{cov}(A,\ B) - \text{cov}(A,\ C) - \text{var}(B),$$

where var denotes variance and cov covariance. Estimated environmental variance of B includes any residual measurement variance; therefore, estimated environmental covariance between chronologically adjacent gain estimates is lowered by the measurement variance of the common weight estimate. Analyses of untransformed data and comparison with measurement variance indicate that some of these correlations are probably still negative after this artifact has been corrected for.

Scale effects and analyses of untransformed data: Data are transformed to remove correlation between mean and standard deviation and to yield an approximately normal distribution (WRIGHT 1968; FALCONER 1981). Because cell multiplication is an exponential process and weight increases greatly with age, we used a logarithmic transformation in the preceding analyses. But this was not always justified. In deciding whether to transform, we attempted to avoid circularity by basing the decision on some criterion other than the pattern to be explained. Although the mean and standard deviation of body weight both increase with age, examining their correlation across ages can confound the phenomenon under study, *i.e.*, changes in variance during growth, with scale effects. To examine the empirical relation between the mean and standard deviation separately from the changes through time, we computed the correlation between means and standard deviations of cross-fostering pairs within each age. Although later ages show significant positive correlations, there is a significant *negative* correlation between mean and standard deviation at early ages in untransformed data. For transformed data, later positive correlations have been eliminated, but early negative correlations are stronger than for untransformed data. During

TABLE 5

Components of phenotypic variance of untransformed mouse weights

Age (wk)	$V_A \pm$ SE	$V_M \pm$ SE	$V_E \pm$ SE	$V_P \pm$ SE	Heritability (%)
			Males		
2	272 ± 53	736 ± 72	145 ± 34	1153 ± 80	24
3	885 ± 179	1488 ± 163	617 ± 121	2989 ± 203	30
4	2140 ± 446	3624 ± 414	1522 ± 302	7287 ± 513	30
5	1417 ± 389	1894 ± 280	1821 ± 279	5132 ± 395	28
6	1236 ± 364	1125 ± 217	1845 ± 264	4206 ± 342	29
7	1548 ± 421	962 ± 229	2109 ± 309	4619 ± 385	34
8	1537 ± 468	1021 ± 258	2556 ± 351	5114 ± 435	30
9	1658 ± 616	699 ± 308	3720 ± 472	6077 ± 564	27
10	2283 ± 734	474 ± 340	4153 ± 561	6910 ± 656	33
			Females		
2	310 ± 59	789 ± 76	145 ± 38	1243 ± 85	25
3	964 ± 168	1417 ± 148	370 ± 107	2750 ± 183	35
4	1852 ± 323	2206 ± 255	776 ± 209	4834 ± 329	38
5	1255 ± 313	1535 ± 221	1373 ± 225	4164 ± 315	30
6	1336 ± 329	1062 ± 192	1454 ± 237	3853 ± 305	35
7	1975 ± 399	1178 ± 215	1453 ± 275	4605 ± 349	43
8	2016 ± 475	995 ± 239	2096 ± 338	5107 ± 414	39
9	2712 ± 588	1450 ± 304	2374 ± 414	6536 ± 513	41
10	2484 ± 623	1753 ± 351	2931 ± 450	7169 ± 571	35

V_A = additive genetic variance; V_M = postnatal maternal variance; V_E = environmental variance; V_P = phenotypic variance. Variances in units of grams^2 have been multiplied by 10^3.

exponential growth, the distribution of age-specific weights changes from left-skewed to right-skewed. Appropriate transformation and measurement scales for these data depend upon the age of the mice.

Analysis of untransformed data shows that log transformation did affect the relative magnitudes of variance components. As can be seen in Table 5 and Figure 3, the maternal component for untransformed data still exhibits marked compensatory growth. Genetic variance peaks at 4 wk and then decreases for 1 or 2 wk. It does not again reach the 4-wk magnitude until 7 wk in females or 10 wk in males. This later increase is not apparent in the log-transformed data but is nearly identical with that found by RUTLEDGE *et al.* (1972), who studied body weight in this strain of mice in another laboratory. In the absence of compensatory growth, variance should never decrease, as each period of growth can then only add to variance already present. Increased genetic variance after 6 wk for untransformed, but not for transformed, data suggests that gain during this period is a function of genetic variance in weight achieved before 6 wk of age: absolute gain after 6 wk is heritable; relative gain is not.

Only for environmental variance can the presence of compensatory growth in the untransformed data be seriously doubted. Although this variance does not decrease, it does reach a temporary plateau. This constancy of variance, despite very rapid increase of the mean, points to a negative association between size

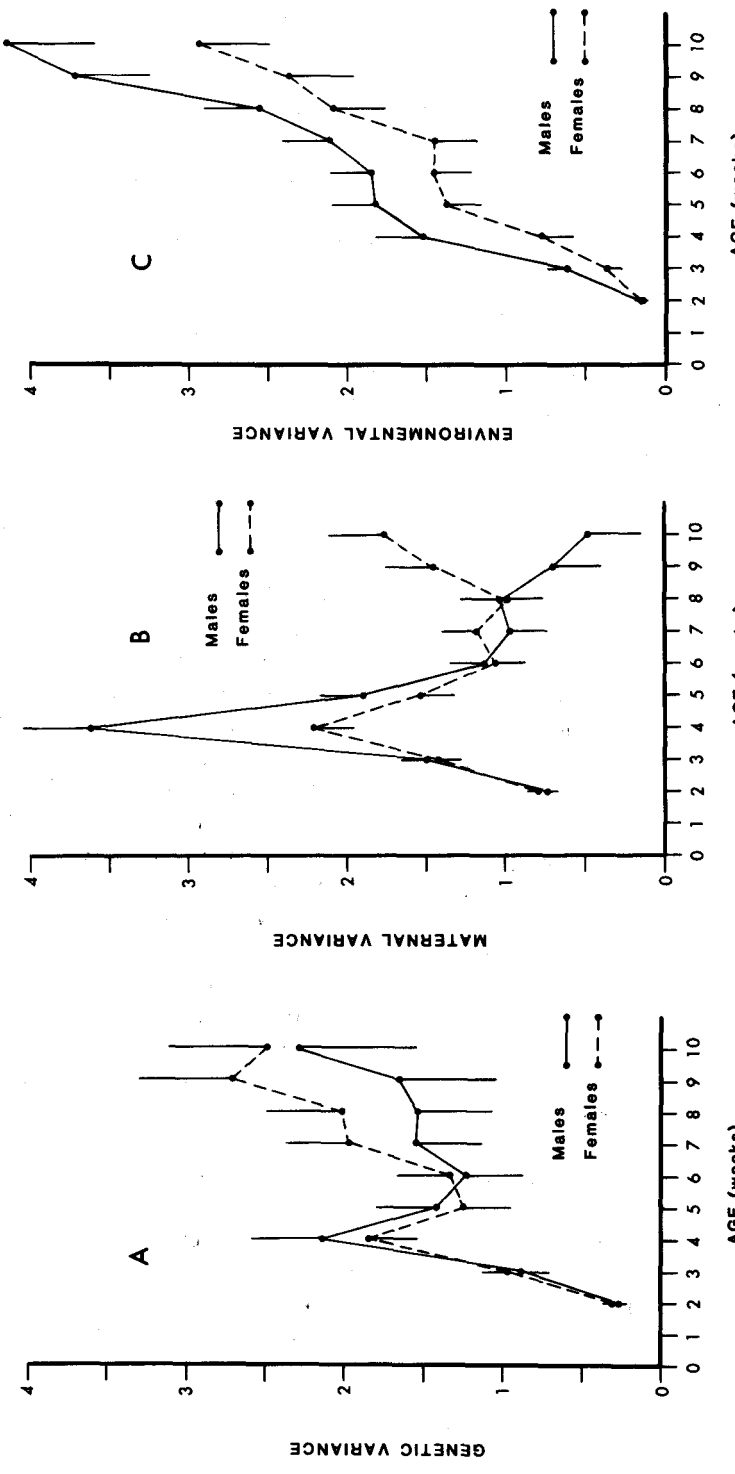

FIGURE 3.—Components of phenotypic variance of untransformed body weight as a function of age. Vertical bars represent 1 SE. A, Additive genetic variance; B, postnatal maternal variance; C, residual environmental variance.

and proportional growth rate. We believe that this pattern indicates compensatory growth in the environmentally determined portion of body weight. RUTLEDGE *et al.* (1972) found that environmental variance decreased between 4 and 5 wk before increasing again. MONTEIRO and FALCONER (1966) also reported compensatory growth in maternal and environmental components of untransformed body weight but not in genetic variance. Their study emphasized maternal variance, however, and our estimates of genetic variance never differ from theirs by as much as one of their standrad errors.

We conclude that convergent growth is not an artifact of logarithmic transformation, since it appears to some extent in all components of variance in untransformed data. The effect is much more apparent in log-transformed data, as expected from the fourfold increase in mean body weight during the period of growth studied and the exponential nature of much of this growth. Although masked by scale effects, compensatory growth can still be detected by analysis of untransformed data.

Convergent growth can be masked by addition of new variance. Postnatal mothers, removed when their litters are 3 wk of age, do not affect divergent growth after 4 wk. Genetic and environmental factors, however, can continue to act throughout life. Although early variance caused by genetic and environmental differences in growth rate is later reduced, additional variation continues to accrue from currently active genetic and environmental sources. This is shown by Figures 4 and 5, which depict portions of variance in body weight at each age that can be statistically explained by variation in the same component at earlier ages. The variance explained by early ages clearly demonstrates effects of both positively and negatively correlated growth. In the genetic component for males (Figure 4A), variance explained by weight at 2 and 3 wk increases between 3 and 4 wk because of positively correlated growth and then decreases rapidly because of negatively correlated growth. This is similar to the pattern shown by maternal variance, the source of which was removed at 3 wk. For the maternal component, there appears to be no significant growth after 3 wk that is not correlated with 2- and 3-wk weights (Figures 4B and 5B).

Compensatory growth is also masked by added variance in the environmental component. In males, for example, Figure 4C indicates that growth between 6 and 7 wk added 0.60 g^2 to environmental variance, whereas half that much was removed from variance already present at 6 wk. Growth between 6 and 7 wk thus yielded a net increase in environmental variance, although this growth was negatively correlated with, and reduced variance resulting from, earlier periods of growth. Existing environmental variance was reduced, but new differences also appeared.

Prenatal maternal effects: Our estimates of genetic variance include any prenatal maternal variance. This component is probably small and not the cause of convergent growth in our genetic estimates. We have examined the effect of litter size at birth, a potentially important prenatal factor, on body weight at each age. Since litter size was standardized at birth, it should have no direct postnatal effect. When included in a linear model, litter size explains only a minute fraction of variance in sex-corrected body weight at 2 wk of age and

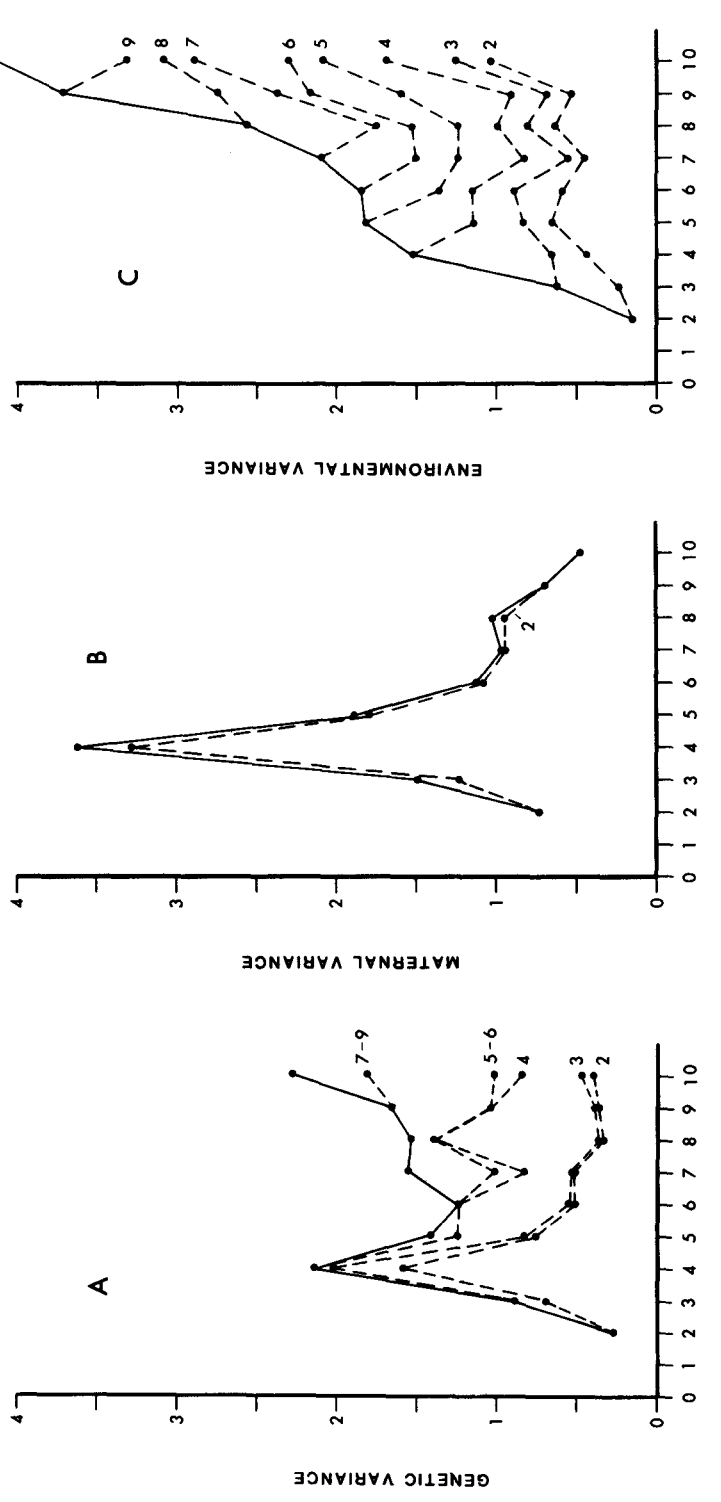

FIGURE 4.—Components of phenotypic variance of untransformed body weights of male mice, decomposed into portions statistically explained by regression on corresponding components at earlier ages. Solid lines are estimates of variance components at ages specified on abscissa. Dashed lines are estimates of portions of variance, at ages specified on abscissa, that can be explained by partial regression on ages specified at ends of dashed lines and all earlier ages. A, Additive genetic variance; B, postnatal maternal variance; C, residual environmental variance.

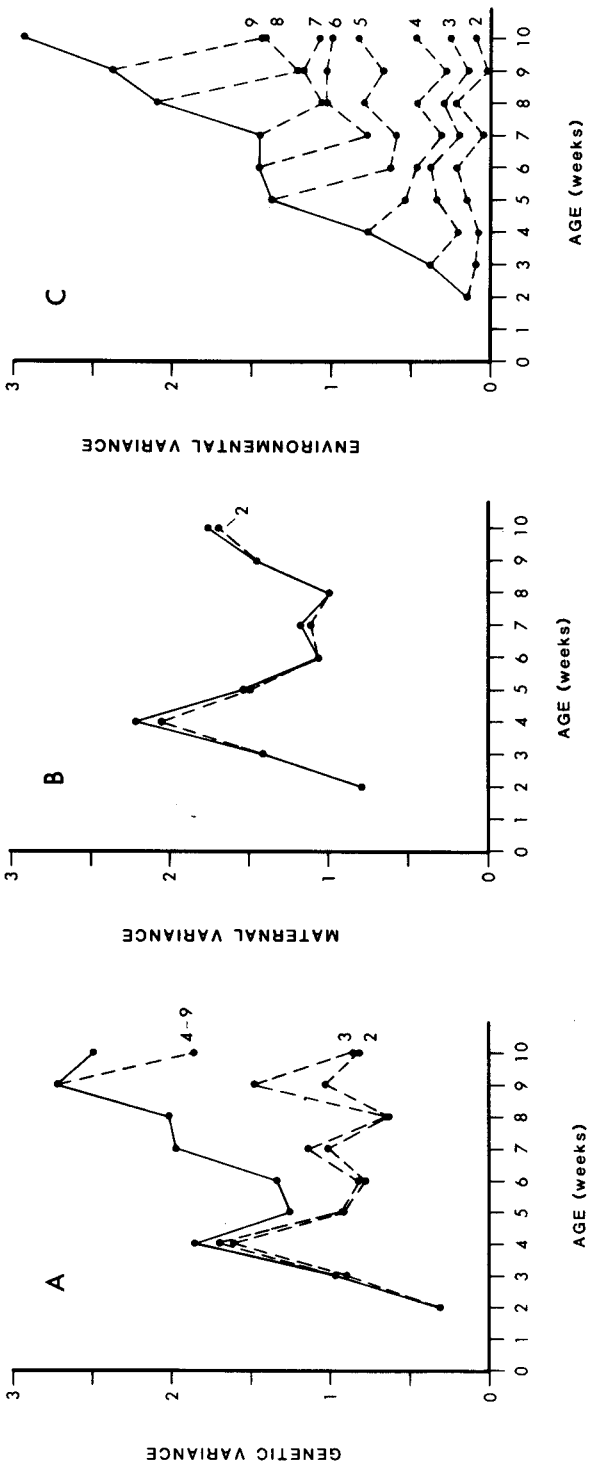

FIGURE 5.—Same as Figure 4, but for female mice. A, Additive genetic variance; B, postnatal maternal variance; C, residual environmental variance.

later, usually less than 1 and not more than 2%. RUTLEDGE *et al.* (1972) reported that litter size at birth had a significant effect on weight at 0, 3 and 9 days but not at 12 days or later; therefore, prenatal maternal effects are probably eliminated by compensatory growth occurring very early in life. Similar conclusions on the importance of prenatal maternal effects were reached by MOORE, EISEN and ULBERG (1970). The apparent unimportance of prenatal maternal factors in all of these studies might result from the *ad libitum* feeding and uniform environment to which mothers were subjected.

We have also analyzed half-sib data from PARRAT (1983), which yields estimates of additive genetic variance uncontaminated by prenatal maternal and dominance variance. These body weight data for Quackenbush mice show compensation in genetic variance much like that reported here. Changes in prenatal maternal and dominance variance are probably not important contributors to these patterns.

THEORETICAL ASPECTS OF CORRELATED GROWTH

Convergent and divergent growth, as represented by correlations between weekly weight gains, are helpful in understanding changes in components of phenotypic variance and correlation during growth. For variance components, this can be seen by decomposing genetic variance at different ages into portions directly attributable to variance in weight gain and portions jointly determined by covariance between gains occurring at different times. Because weight at any age is the sum of all previous weight gains, variance in weight at age t,

$$\text{var}(W_t) = \sum_{i=1}^{t} \text{var}(G_i) + 2 \sum_{i=2}^{t} \sum_{j=1}^{i-1} \text{cov}(G_i, G_j),$$

where var denotes variance, cov covariance, W_t weight at time t and G_i gain during interval i, prior to time t. If gains were uncorrelated, the first term would completely determine variance of weight. If weekly gains were all positively correlated, as would be the case if ranking of families by growth rate were constant through time, var(W_t) would always be greater than the summed variances of gains. Small differences in gains, if positively correlated with pregain weight, can cause large increases in variance. Similarly, a large variance in weight can be disproportionately reduced by minor differences in gain, provided that gain is negatively correlated with weight. Because covariance between growth and initial weight can be much larger than the variance of growth, weekly change in variance of weight can be much larger than would be predicted from the variance of growth during that week.

Figure 6 shows the effect of correlated gains on genetic variance. In males, positively correlated gains during the first several weeks cause genetic variance of weight to exceed that directly determined by the variance of gains, but subsequent negatively correlated gain reduces variance to less than that predicted from summing the variances of gains, and the deficit persists for several weeks. The pattern is similar in females, but genetic variance never decreases below the portion attributable to variance of gain.

Serial correlation between weights can also be analyzed in terms of a contribution from variance of gains and a contribution from covariance of gains. If

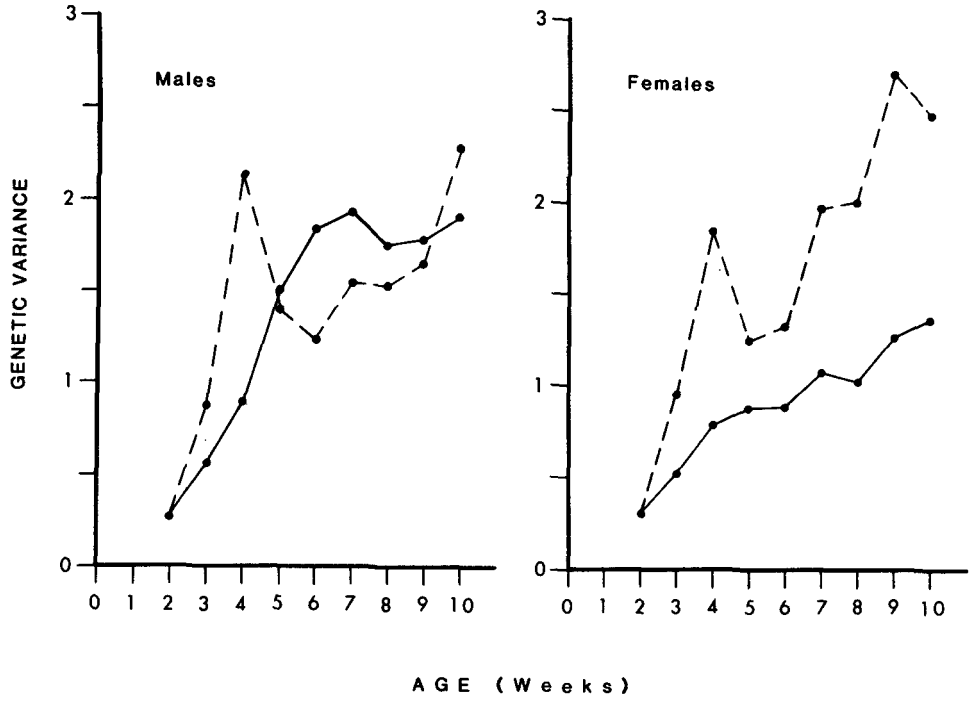

FIGURE 6.—Effects of targeted growth on genetic variance. Solid line is estimate of genetic variance in untransformed body weights expected from the summation of the genetic variances of weekly gains. Dashed line is the observed genetic variance of weight. Difference results from genetic covariance between gains.

gains 1 through N contribute to weight at time X (W_x), and gains 1 through N and $N + 1$ through M contribute to weight at a later time Y (W_y), then the correlation between W_x and W_y,

$$r_{xy} = \frac{\sum_{i=1}^{N} \text{var}(G_i) + 2 \sum_{i=2}^{n} \sum_{j=1}^{i-1} \text{cov}(G_i, G_j)}{\sqrt{\text{var}(W_x)\ \text{var}(W_y)}} + \frac{\sum_{i=1}^{N} \sum_{K=N+1}^{M} \text{cov}(G_i, G_k)}{\sqrt{\text{var}(W_x)\ \text{var}(W_y)}},$$

where G_i is gain during interval i. The numerator of the first term is equal to $\text{var}(W_x)$, and if pre- and post-X growth are uncorrelated (*i.e.*, when $\sum \text{cov}(G_i, G_k) = 0$),

$$r_{xy} = \sqrt{\frac{\text{var}(W_x)}{\text{var}(W_y)}}$$

The numerator of the second term is the portion of covariance between W_x and W_y caused by correlation between pre- and post-X gains. Covariance between

any two weights can thus be additively partitioned into a portion due to shared growth and another portion due to correlation between shared and later, unshared, growth. The latter portion represents the effect of convergent or divergent growth occurring between times X and Y.

Although covariance can be additively partitioned, division of the covariance by the geometric mean of the variances, to obtain the correlation, destroys additivity because convergent and divergent growth between times X and Y affect the variance of W_y:

$$\begin{aligned}\operatorname{var}(Wy) &= \operatorname{var}(W_x) + \sum_{K=N+1}^{M} \operatorname{var}(G_k) + 2 \sum_{K=N+2}^{M} \sum_{L=1}^{K-1} \operatorname{cov}(G_k, G_L) \\ &+ \quad 2 \sum_{i=1}^{N} \sum_{K=N+1}^{M} \operatorname{cov}(G_i, G_k) \\ &= \operatorname{var}(W_x) + \operatorname{var}(\text{new gain}) + 2 \operatorname{cov}(W_x, \text{new gain}),\end{aligned}$$

and so

$$r_{xy} = \frac{\operatorname{var}(W_x) + \operatorname{cov}(W_x, \text{new gain})}{\sqrt{\operatorname{var}(W_x)\,[\operatorname{var}(W_x) + \operatorname{var}(\text{new gain}) + 2 \operatorname{cov}(W_x, \text{new gain})]}}.$$

Figure 7 shows the effect of continued growth on r_{xy} for different values of

$$r_{Wx,\,\text{new gain}} = \frac{\operatorname{cov}(W_x, \text{new gain})}{\sqrt{\operatorname{var}(W_x)\operatorname{var}(\text{new gain})}},$$

assuming an initial variance of 1, *i.e.*, $\operatorname{var}(W_x) = 1$. When initial weight and subsequent gain are uncorrelated, the curve depicting r_{xy} has the form $1/\sqrt{T}$, where T = total variance. This curve decreases less rapidly as variance is added, approaching a theoretical asymptote of zero as T approaches infinity, but decrease in r_{xy} is very slow beyond a fivefold increase in variance, at which time r_{xy} is about 0.4. When $r_{Wx,\,\text{new gain}}$ is positive, decrease in r_{xy} is slower. If $r_{Wx,\,\text{new gain}}$ is near 1, r_{xy} stays very near unity for all reasonable values of added variance in growth. Moderately negative values of $r_{Wx,\,\text{new gain}}$ accelerate the decrease in r_{xy}, because such growth both adds "random" variation (with respect to W_x) and decreases variance that was generated before time X, the variance of growth shared by W_x and W_y.

The most interesting behavior of r_{xy} occurs when $r_{Wx,\,\text{new gain}}$ is strongly negative, *e.g.*, -0.9 or less. One might expect such growth to quickly reduce r_{xy}, as it rapidly destroys the variance generated during the pre-X period of common growth. But r_{xy} also depends upon $\operatorname{var}(W_y)$, and when $r_{Wx,\,\text{new gain}}$ is strongly negative, reduction of $\operatorname{cov}(W_x, W_y)$ is only slightly more rapid than reduction of $\operatorname{var}(W_y)$. This is because very little "random" variation is being added to $\operatorname{var}(W_y)$, as time passes, to compensate for the elimination of variance that was generated during pre-X growth. In the extreme case, when $r_{Wx,\,\text{new gain}}$ equals -1, the pattern of dispersion of weights at time X is maintained until the variance in new gain is equal to $\operatorname{var}(W_x)$. During this time, growth curves maintain the same pattern of relative distances from each other (no "random" variation is added), but they are converging. When they finally converge, the variance in weight is zero, and r_{xy}

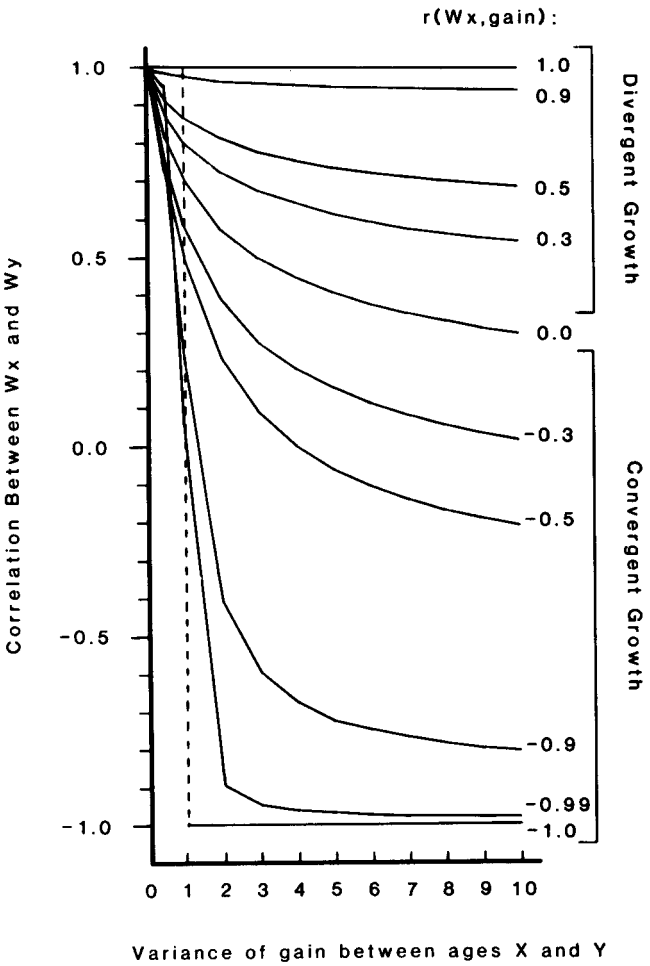

FIGURE 7.—Predicted effects of convergent and divergent growth on serial autocorrelation of body weight. Vertical axis is predicted correlation (r_{xy}) between weight at age X (W_x) and at subsequent age Y (W_y), as a function of variance of gain between ages X and Y. One unit of variance of gain (horizontal axis) is equal to the variance of W_x. Curves show predicted r_{xy} for different values of the correlation between W_x and gain between ages X and Y. Dashed vertical line represents undefined r_{xy} changing from positive to negative unity.

changes from +1 to undefined. If this pattern of growth continues, r_{xy} becomes −1 as soon as the variance of weight becomes positive again. In this case, convergent growth, relative to time X, has become divergent growth, relative to the time at which the growth curves cross. Compensatory growth has then overcompensated for the initial divergence at time X.

Strong negative correlations between gains can thus cause large and rapid fluctuations in the serial correlation of traits measured at different ages. Because serial genetic autocorrelation causes correlated responses at other ages when selection is applied to age-specific traits, modification of genetic autocorrelation by convergent growth might be an important aspect of the evolution of developmental systems.

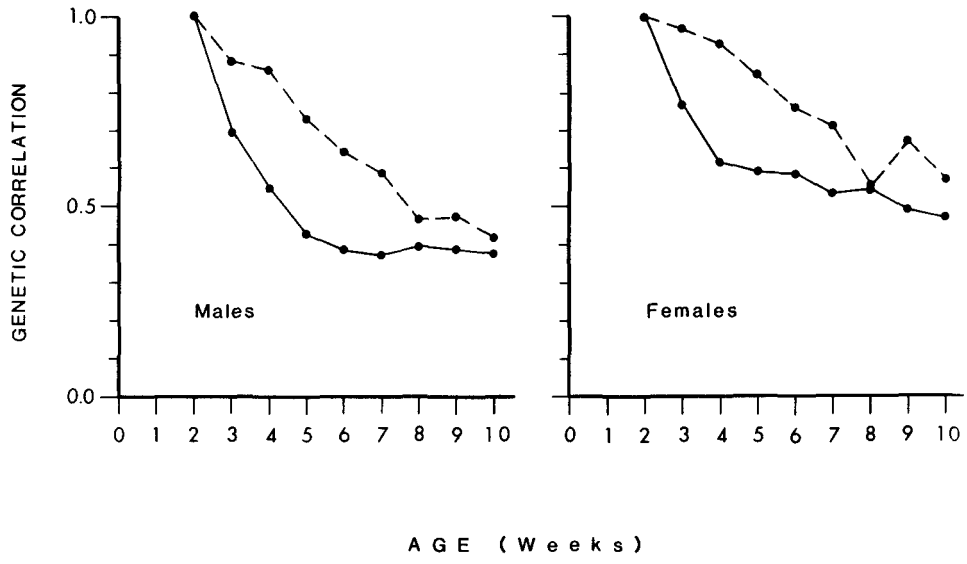

FIGURE 8.—Effects of targeted growth on genetic serial autocorrelation of weight at 2 wk of age with weight at later ages. Solid line is genetic correlation predicted by genetic variance of gain between ages. Dashed line is estimate of actual genetic correlation. Difference results from genetic covariance between weekly gains.

Figure 8 shows the effect of correlated growth on additive genetic correlation between 2-wk and subsequent untransformed weights in the mice. Genetic correlation at first decreases less rapidly than predicted from variance of growth because of divergent growth prior to 4 wk of age. Convergent growth then accelerates the decline, so it nearly overtakes the predicted value. On average, divergent growth appears to have been more important than convergent, as genetic correlation is always higher than that predicted from uncorrelated gains.

DISCUSSION

Our analyses of body weights are best summarized by the concept of targeted growth: all components of phenotypic variance increase early in life, then are reduced as growth trajectories converge upon a "target window" near the end of exponential growth. This is often followed by divergence during the linear phase. In general, if growth rates vary but cessation or slowing of growth depends upon weight achieved, rather than age, then this growth-limiting mechanism can cause targeted growth.

Targeted growth affects all sources of variation (genetic, maternal and environmental), so the explanation must not be limited to a single component. Because strong selection for increased weight gain is simultaneous selection for gain at all previous age intervals, this could be expected to result in negative genetic correlations between component gains (FALCONER 1981, p. 300). This alone, however, does not explain the corresponding pattern in maternal and environmental correlations, unless processes that might link different components of variance are invoked. For example, if maternal or environmental variance occurs as "noise" around a genetically controlled process, then the more genetically variable components of the process could also have higher

maternal or environmental variances. If maternal factors merely provide different environments in which potential maximum growth rates differ, but the potential is expressed only when genetically determined growth rate is high, then increased genetic variance should be paralleled by increased maternal variance. This implies a genetic-maternal interaction and probably multiplicative rather than additive combination of effects, but genetic-maternal interaction is estimable in our cross-fostering design, and it appears to be negligible. Any such interaction is included in the residual environmental component here. Multiplicative effects are made additive by log transformation. Thus, we find little evidence for this selection-interaction hypothesis.

The simplest hypothesis is a general regulatory mechanism for body size: one that operates upon body size or its components directly, without distinguishing genetic from other sources of variation in early growth rate. In this model, genetic or environmental variance in early growth rate elicits negative feedback from the growth-regulating mechanism. This assumes a degree of separation between genetic factors directly affecting growth rate and those determining the "target" value. Thus, some genetic differences would mimic environmental differences by appearing as deviations from targeted size, to be corrected by the regulatory mechanism. Other genetic differences might change the target value or otherwise modify the regulatory system. A similar separation was suggested by DICKINSON (1960) in the contrast between "juvenile growth potential" and "genetic growth competence," the former influencing growth rate and the latter final weight. Such separation is also implicit in successful selection for growth curve shape (MCCARTHY and DOOLITTLE 1977) and imperfect genetic correlation between mature weight and age at maturity (TAYLOR and FITZHUGH 1971; FITZHUGH 1976). Separation between rate parameters and the timing of growth initiation or cessation is also a common theme in theories relating evolutionary and developmental change (*e.g.*, ALBERCH *et al.* 1979).

The physiological basis for convergent growth at the end of the exponential phase is probably size-dependent initiation of puberty (FRISCH 1974). MONTEIRO and FALCONER (1966) showed that vaginal opening in their mice occurred at different ages but at nearly the same weight in all mice. FRISCH and REVELLE (1971) proposed that puberty is triggered by achievement of a particular weight. This hypothesis was later modified to predict pubertal onset at a particular fat to lean body composition that is highly correlated with weight in most cases (FRISCH 1980; SIZONENKO 1981; see also JOHNSTON *et al.* 1975; CRAWFORD and OSLER 1975). Puberty causes a growth spurt but also eventually reduces growth. By occurring at a particular body weight or composition, puberty will cause adult size to be similar in mice that grew at different rates. Positive correlations between early and later weights in our data, as well as persistence of maternal effects in postpubertal mice, show that not all variation in early growth rate is "compensated" by timing of puberty. Final size may be determined by an antagonistic balance between rate and duration of growth.

Early growth rates may have their own regulatory mechanisms as well. TANNENBAUM, GUYDA and POSNER (1983) report a negative feedback system in-

volving body weight, growth hormone, somatomedins and appetite. Also, adult size in some tissues is thought to be maintained by chalones, tissue-specific mitotic inhibitors (BULLOUGH 1975). Thus, prepubertal "catch-up" growth following temporary starvation or illness, regulation of adult size by timing of puberty and maintenance of adult tissue mass may all be governed by different, but interrelated, regulatory mechanisms.

Early growth in rats and mice (our exponential phase) is primarily by cell multiplication with less increase in cell size; later growth (our linear phase) is primarily by increased cell size with little increase in number (FALCONER, GAULD and ROBERTS 1978; ENESCO and LEBLOND 1962; WINNICK, FISH and ROSSO 1968; CHEEK *et al.* 1971; CHEEK 1975). Targeted growth in our mice has probably involved regulation of cell numbers. Portions of variance explained by early weight in Figures 4 and 5 may correspond to variation in cell numbers, whereas later increments in variance probably result from differences in cell size. The slightly longer period of divergent growth in our data for males is compatible with later onset of puberty in that sex. Puberty in males also involves more extensive cell multiplication than in females (CHEEK 1974).

FALCONER, GAULD and ROBERTS (1978) found that cell number not only stopped increasing but also declined markedly in several organ systems in mice near the end of exponential growth. These organs continued to increase in size because cell size increased. Death of particular cell populations could contribute to targeted growth. Although essential for limb-bud differentiation (RAFF and KAUFMAN 1983) and brain development (ZAMENHOF and VAN MARTHENS 1979; RAKIC and RILEY 1983), the extent and importance of cell death in general growth and size regulation is unknown.

We thank DONNA and MARIA VAN HORN and RICK MUNSON for excellent technical assistance in the laboratory. JAMES N. CHEVERUD, JAMES F. CROW, AURORA GARCIA-DORADO, LUCI ANN P. KOHN, H. BRADLEY SHAFFER and JUDY SILVERSTEIN provided helpful comments on the manuscript. This research was supported by the National Science Foundation (DEB-8109904) and by the College of Agriculture and Life Sciences of the University of Wisconsin, Madison.

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