THE RELATIONSHIP OF GENOTYPE, SEX, BODY WEIGHT, AND GROWTH PARAMETERS TO LIFESPAN IN INBRED AND HYBRID MICE*

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SUMMARY

Data from nine inbred and six hybrid mouse strains of both sexes were used in a correlational analysis to examine the relationships between lifespan and several growth parameters, including body weight at weaning, at 6 weeks after weaning, and at 1 year, and estimates of growth rate, food consumption, and feeding efficiency during early life. The analysis revealed strong relationships of genotype to all variables. Hybridization was associated with longer lifespan, but sex was not related to lifespan. Several growth parameters were significantly related to lifespan, but the directions of the correlations were sex-dependent. Several body weight and growth parameters were positively correlated to lifespan in males, while negatively correlated to lifespan in females. Genotype accounted for most of the variance in these relationships with the exception of hybrid males, where the correlation between growth rate and lifespan was attributable largely to environmental factors. In demonstrating significant correlations between lifespan and constitutional variables within a species, the results supported a morphogenetically based hypothesis of lifespan inheritance; however, the sex differential in the direction of the relationship between growth and lifespan further demonstrated the difficulty of making predictions deduced from the hypothesis.

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INTRODUCTION

The marked variability in lifespan among inbred and hybrid strains of house mice (*Mus musculus*) is well documented [1]. The genetic component of this variability is little understood, although estimates have been made of the heritability of lifespan [2–4], the degree of genetic determination [5], and the number of genetic loci possibly involved [5].

One hypothesis for the observed variability in lifespan is that strains differ in their susceptibility to specific disease processes [2, 4, 6]. Another hypothesis concerns the inheritance of specific growth patterns which, through interaction with environmental factors, determine the ultimate length of life [7–9]. This morphogenetically based hypothesis, which is consistent with a classic view in gerontology that senescence begins when growth terminates [10–12], explains lifespan as a by-product of a genetic program of development (see ref. 13 for review).

One prediction from the latter hypothesis is that strains demonstrating slow rates of growth will tend to be long-lived. Apparent confirmation of this prediction is found in studies of mice comparing different strains [8], in studies comparing one strain to its single-gene mutations [7], and in studies comparing divergent lines from selective breeding based on growth rates [14]. Analysis of intra-strain correlations between growth parameters and lifespan in mice [7, 8, 15] and in rats [16–18] also provides evidence to support the hypothesis. Significant negative correlations between growth rate and lifespan in homogeneous mouse strains is offered as additional evidence of the influence of environmental factors upon the genetic program for growth and lifespan [7, 8]. Furthermore, results of studies using environmental manipulations, such as diet or exercise, to retard growth are also offered as evidence to support the hypothesis [16, 18–20].

Conflicting results, however, have emerged from several studies. For example, an early study [21] found no association between lifespan in the rat and growth between 5 and 8 weeks of age. Other studies have observed a positive relationship between growth and longevity in mice [22] and in rats [23, 24]; *i.e.* animals growing more rapidly during certain portions of their lifespan lived longer.

Additional research has focused less upon early growth patterns and more upon ultimate adult body weight parameters, or constitutional variables [25, 26], in relation to the morphogenetic hypothesis of longevity. Inter-species comparisons of adult body weight and brain weight have shown significant positive correlations with lifespan [25]. Regarding mouse strains, the prediction is that animals weighing more as adults should live longer. The results of one analysis of these parameters among 18 inbred mouse strains failed to support this prediction [26], while those of another, using progenitor and hybrid mouse strains, supported the prediction that strains with higher adult body weights tend to live longer [3]. This positive relationship has also been observed within groups of homogeneous mouse strains [7, 8], homogeneous rat strains [27], and heterogeneous rat strains [16, 23].

The present analysis was conducted to provide additional data in mice pertaining to the hypothesis linking constitutional factors to lifespan. Growth characteristics, as measured by changes in body weight over specified intervals, were examined in inbred and hybrid strains. Both males and females of each strain were observed. Data were also available on the amount of food consumed during the first 6 weeks following weaning, which permitted estimates of feeding efficiency. Thus, the present analysis applied a multivariate correlational approach to examine the relationship between longevity and various growth parameters in mice of identified genotypes.

MATERIALS AND METHODS

The sample of nine inbred and six hybrid mouse strains (*Mus musculus*) studied is shown in Fig. 1. Each inbred and hybrid strain comprised 60 mice, 30 males and

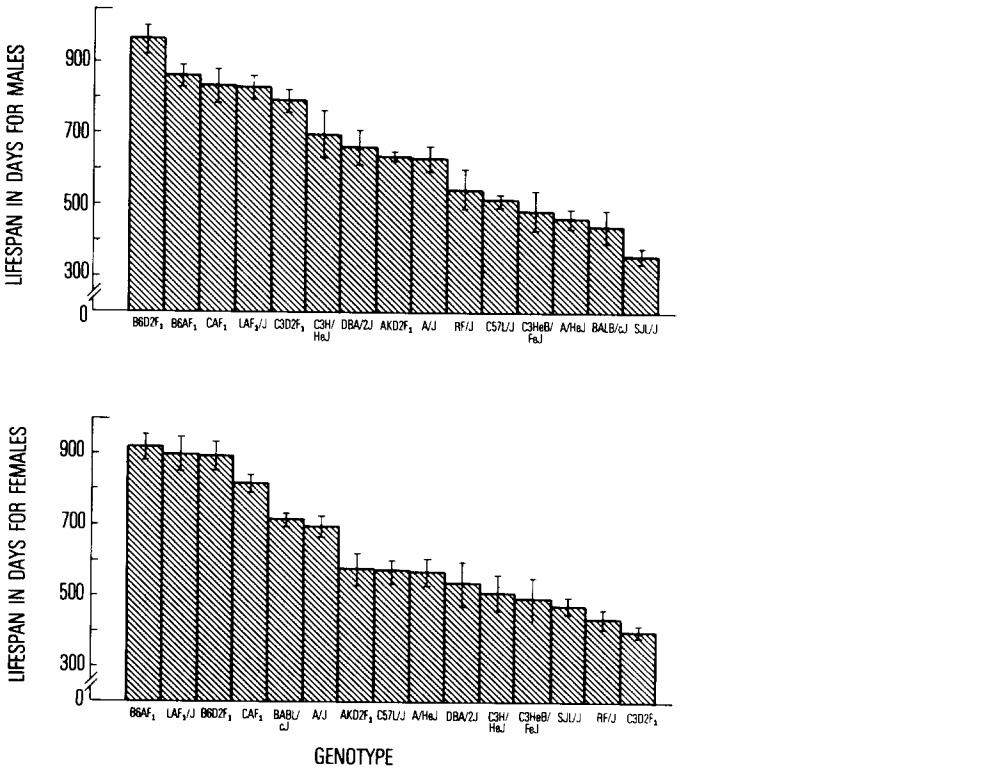

Fig. 1. Rank order of mean lifespans for inbred and hybrid mice of both sexes. Each mean ± S.E.M. is estimated for 30 mice. These estimates vary from an earlier report of mean lifespan in these strains attributed to the third author [1], because no probit transformation has been applied. Parental strains of hybrid designations are as follows (♀ × ♂): $AKD2F_1$ = AKR/J × DBA/2J; $B6AF_1$ = C57BL/6J × A/J; $B6D2F_1$ = C57BL/6J × DBA/2J; CAF_1 = BALB/cJ × A/J; $C3D2F_1$ = C3H/HeJ × DBA/2J; LAF_1 = C57L/J × A/HeJ.

30 females, for a total of 900 mice. All hybrid mice were obtained from the Animal Resources Division of the Jackson Laboratory at weaning, when they were 3 weeks old. All inbred mice were obtained from the same source at weaning when they were 4 weeks of age. Two exceptions were the C3H/HeJ and C3HeB/FeJ strains which were weaned at 3 weeks.

The day after weaning, the mice were weighed and were randomly assigned to cages. To maximize the efficiency of the experimental design, animals of the same sex and strain were housed five together, thereby partitioning each strain into 12 sample groups. Housing consisted of standard steel cages (28 X 12.7 X 14.6 cm) with sterilized wood shavings for bedding. Commercial, pasteurized food (Old-Guilford 96WA, 24% protein) was provided *ad libitum* in hoppers attached to the steel-mesh cage cover. Chlorinated–acidified water (15 parts per million residual chlorine from sodium hypochlorite and pH 2.5 from hydrochloric acid) was provided *ad libitum* from water bottles fitted with rubber stoppers and stainless steel tubes.

The cages were placed in a separate room that was ventilated with about six changes of fresh air per hour. The experiment was begun during the summer months when the room temperature ranged between 23 °C during nightime hours and 32 °C during daytime hours. The photoperiod was set at 0600 to 1800 hours and provided illumination of at least 52.8 milliphots.

The mice were weighed once a week for the first 6 weeks after weaning. Forceps dipped in a disinfectant were used to manipulate the mice to minimize the transference of infectious agents between cages. The amount of food consumed was determined for the first 6 weeks by weighing the amounts provided and remaining between weighings each week. Fresh cages, food, and water were supplied weekly. Dead mice were removed from the cages as they were discovered, and the date was recorded. All surviving mice were weighed again at 1 year of age.

Mice within each cage were not identified individually. Instead, each group of five mice allowed a sample mean to be computed. Thus, it was possible to obtain 12 sample means for each strain. The anticipated stability and distribution of sample means was felt to more than compensate for the reduction in the degrees of freedom and associated power of the statistical analysis of the data.

The variables used in the correlational analysis are defined in Table I.

RESULTS

As observed in Fig. 1, a substantial range existed in the mean lifespan of mouse strains in this sample. The intercorrelation matrix of variables is presented in Table II. As expected, GENO was significantly related to all the variables and thus provided a powerful index which discriminated among strains on the basis of body weight, food intake, and growth rate measures. The correlation between GENO and LS was also substantial. Genotype accounted for over half the variance in lifespan, $R^2 = 0.58$, this statistic being computed as the square of the multiple correlation coefficient, R.

TABLE I

DEFINITION OF VARIABLES

Variable abbreviation	*Definition*
GENO	Genotype or strain
SEX	Sex
HYB	Hybrid-inbred designation
LS	Lifespan (in weeks)
BWW	Body weight (in grams) at weaning
BW6	Body weight (in grams) 6 weeks after weaning
BW1Y	Body weight (in grams) at 1 year of age
GR1	(BW6 – BWW)/6
GR2[a]	Natural log of BW1y – natural log of BWW/X
EFF	(BW6 – BWW)/FOOD
FOOD	Weight (in grams) of food consumed from weaning to week 6

[a] In the formula for GR2, $X = 43$ (weeks) for all hybrid strains and two inbred strains, C3H/HeJ and C3HeB/FeJ; for all other inbred stains, $X = 42$ (weeks).

Consistent with statistical methods in past studies [2–4], the genetic determinant of lifespan was also estimated in terms of heritability (in the broad sense) at $h^2 = 0.41$, which represents the fraction of the total or phenotypic variance attributable to genetic variance.

As a genetic variable, SEX was also highly related to each of the growth indices, with the exception of GR2 (the growth rate between weaning and 1 year). All the correlation coefficients were negative, indicating that female mice tended to weigh less at weaning, at 6 weeks after weaning, and at 1 year, and that they had slower growth rates, ate less, and exhibited less feeding efficiency than did male mice. Interestingly, there was no significant relationship between SEX and LS. As shown in Fig. 1, in only half the strains did the mean lifespan of females exceed that of males.

As the third genetic factor, HYB also accounted for a significant degree of the variation among several growth variables, including BWW, GR1, and EFF. Compared to inbred strains, the hybrids tended to weigh more at weaning, added body weight at a faster rate for the first 6 weeks after weaning, and showed greater efficiency in feeding. Hybridization also meant generally longer lifespans, as the relationship to lifespan was positive and significant ($r = 0.48$, $p < 0.001$). This hybrid vigor is evident in Fig. 1, which shows that long-lived mice tended to be from hybrid strains.

Examining the relationship between lifespan and the growth measures, we found only three—BWW, BW1Y, and GR2—to be significantly related to lifespan. The longest living mice tended to weigh more at weaning and at 1 year; they also had the highest growth rate during this period. The relationship between lifespan and food intake for the first 6 weeks after weaning was also significant but not substantial ($r = 0.15$, $p < 0.05$). Other interesting relationships between food intake and body weight parameters can be observed in Table III but will not be discussed here.

TABLE II

INTERCORRELATION MATRIX OF GROWTH RATE AND FOOD CONSUMPTION MEASURES, GENOTYPE, AND LIFESPAN FOR MALE AND FEMALE MICE OF 15 INBRED AND HYBRID STRAINS (n = 180)

Variable	*Correlation coefficients*[a]										
	GENO[b]	*SEX*[c]	*HYB*[c]	*LS*	*BWW*	*BW6*	*BW1Y*	*GR1*	*GR2*	*EFF*	*FOOD*
GENO	1.00	–									
SEX	–	1.00									
HYB	–	–	1.00								
LS	0.76***	0.02	0.48***	1.00							
BWW	0.84***	−0.31***	0.43***	0.19**	1.00						
BW6	0.41**	−0.78***	−0.05	0.07	0.31***	1.00					
BW1Y	0.59***	−0.17*	0.08	0.34***	0.08	0.42***	1.00				
GR1	0.79***	−0.36***	0.34***	0.11	−0.63***	0.53***	0.26***	1.00			
GR2	0.41**	−0.10	0.08	0.45***	−0.21**	0.08	0.81***	0.25***	1.00		
EFF	0.77***	−0.37***	0.35***	0.14	−0.61***	0.51***	0.27***	0.96***	0.28***	1.00	
FOOD	0.53***	−0.61***	−0.14	0.15*	0.34***	0.83***	0.32***	0.36***	−0.02	0.21**	1.00

[a]Pearson product-moment correlation coefficients (r), except as noted in b.
[b]Genotype is a categorical variable; therefore, the r's associated with this variable actually represent coefficients of multiple correlation. As such, they provide no information as to the direction of a relationship. Moreover, the degrees of freedom associated with the tests of significance for these r's are *not* the same as for the r's associated with the other variables.
[c]For the categorical variable sex, males are coded zero, females, one; for inbred-hybrid designation, inbred strains are coded zero, hybrid strains, one.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

Since sex and hybridization were both genetic factors highly related to many growth measures, it was difficult to assess from this analysis alone the independent relationship between lifespan and the other variables. Therefore, separate correlational matrices were generated for males and females of both inbred and hybrid strains, for a total of four matrices, as shown in Table III.

Again we observed a strong relationship between genotype and all other independent variables in all groups except male hybrids. In this group genotype was highly related to all variables except BW6, BW1Y, and GR2. A strong relationship between GENO and LS emerged in all groups. Genotype accounted for about half the variance in lifespan among male inbred, female inbred, and male hybrid mice (R^2 = 0.52, 0.47 and 0.43, respectively). Among female hybrid mice, the relationship was even stronger (R^2 = 0.81).

Of primary interest were the relationships of body weight, food intake, and growth rate measures to lifespan within each group. Estimates of growth rate (GR1 and GR2) were significantly and positively related to lifespan for males of both inbred and hybrid strains. The only exception was the absence of a relationship between GR1 and lifespan for hybrid males. In contrast, several estimates of growth rate were significantly but negatively related to lifespan for females of both inbred and hybrid strains. The relationship between GR2 and lifespan for females of inbred strains, although negative, failed to reach the conventional level of significance ($r = -0.21, p > 0.05$).

TABLE III

INTERCORRELATION MATRIX OF GROWTH RATE AND FOOD CONSUMPTION MEASURES, GENOTYPE, AND LIFESPAN: MALE AND FEMALE MICE OF INBRED AND HYBRID STRAINS

Variables	*Correlation coefficients*								
	GENO	*LS*	*BWW*	*BW6*	*BW1Y*	*GR1*	*GR2*	*EFF*	*FOOD*
Inbred males (n = 54)									
GENO	1.00								
LS	0.72***	1.00							
BWW	0.85***	−0.39**	1.00						
BW6	0.78***	0.12	0.17	1.00					
BW1Y	0.79***	0.41**	−0.04	0.51***	1.00				
GR1	0.82***	0.44***	−0.84***	0.39**	0.33*	1.00			
GR2	0.60**	0.39**	−0.23	0.31*	0.84***	0.40**	1.00		
EFF	0.82***	0.51***	−0.78***	0.36**	0.35**	0.94***	0.44***	1.00	
FOOD	0.78***	−0.23	0.24	0.59***	0.15	0.07	−0.05	−0.21	1.00
Inbred females (n = 54)									
GENO	1.00								
LS	0.67***	1.00							
BWW	0.86***	0.20	1.00						
BW6	0.85***	−0.21	0.09	1.00					
BW1Y	0.93***	−0.13	0.05	0.74***	1.00				
GR1	0.94***	−0.30*	−0.79***	0.54***	0.40**	1.00			
GR2	0.93***	−0.21	−0.45***	0.63***	0.86***	0.76***	1.00		
EFF	0.93***	−0.30*	−0.79***	0.50***	0.31*	0.98***	0.69***	1.00	
FOOD	0.86***	−0.12	0.14	0.80***	0.77***	0.36**	0.61***	0.23	1.00
Hybrid males (n = 36)									
GENO	1.00								
LS	0.66**	1.00							
BWW	0.87***	0.02	1.00						
BW6	0.41	0.04	−0.08	1.00					
BW1Y	0.31	0.73***	0.15	0.32	1.00				
GR1	0.78***	0.03	−0.87***	0.56***	0.04	1.00			
GR2	0.38	0.86***	−0.04	0.26	0.94***	0.17	1.00		
EFF	0.70***	0.15	−0.80***	0.54***	0.10	0.94***	0.26	1.00	
FOOD	0.73***	−0.18	−0.21	0.74***	0.12	0.52***	0.03	0.28	1.00
Hybrid females (n = 36)									
GENO	1.00								
LS	0.92***	1.00							
BWW	0.90***	0.33*	1.00						
BW6	0.76***	−0.23	0.23	1.00					
BW1Y	0.71***	−0.25	0.30	0.29	1.00				
GR1	0.82***	−0.41**	−0.75***	0.46**	−0.11	1.00			
GR2	0.80***	−0.49**	−0.73***	−0.02	0.43**	0.63***	1.00		
EFF	0.80***	−0.51***	−0.75***	0.38*	−0.02	0.94***	0.68***	1.00	
FOOD	0.69***	0.14	0.37*	0.75***	0.09	0.18	−0.29	−0.09	1.00

Note: footnotes to Table II apply here.
*$p \leq 0.05$; **$p \leq 0.01$; ***$p \leq 0.001$.

Paralleling the direction of these relationships was the relationship of feeding efficiency to lifespan within each group, which failed to reach significance only for males of hybrid strains. No significant relationships emerged within any of the groups between total food consumption (FOOD) and LS. Other significant correlations among the variables can be observed in Table III.

Regarding body weight measures, the earliest significant correlate of lifespan was BWW among inbred males and hybrid females. For females of hybrid strains, BWW was positively associated with lifespan, while the relationship in males of inbred strains was negative. Since males of C3H/HeJ and C3HeB/FeJ strains were weaned at 3 weeks, compared to weaning at 4 weeks for other male inbred strains, the possibility existed that the obtained negative relationship between BWW and lifespan simply reflected that males weaned at 3 weeks weighed less but lived longer than males weaned at 4 weeks. When week of weaning was held constant statistically (partial correlation), the correlation between BWW and lifespan was no longer significant ($r = -0.18, p > 0.05$).

There were no significant relationships between LS and BW6 in any group. However, the correlations between LS and BW1Y were significant and positive for male mice, both inbred and hybrids. Although negative in direction, the correlations between BW1Y and LS among females were not significant. Because body weight at two points was used to calculate growth rates, it was not surprising that these variables were often related as can be observed in Table III.

Thus, by dividing the analysis into groups on the basis of sex and inbred-hybrid designation, we still observed that growth rate and body weight were correlated with lifespan, as we had observed in Table II; however, we now saw that the direction of the relationship was dependent upon sex. Yet at this stage of the analysis it was not possible to assess the relationship between lifespan and growth rate with all sources of genetic variability held constant. The effect of genotype remained uncontrolled.

To provide control over genetic variability, we next conducted a hierarchical regression analysis [28] within each group. The summary of these analyses is presented in Table IV. Genotype was entered first in each regression equation to allow for the collective contributions of GR1 and GR2 to lifespan to be examined independent of genotype. GR1 was entered next into each equation, since it provided an estimate of growth rate early in life; while GR2 was entered last, since it provided an estimate of growth rate across the exponential phase of growth for laboratory rodents [29].

The regression analyses clearly indicated that within male and female inbred strains and female hybrid strains, GR1 and GR2 contributed little to the explainable variance in lifespan beyond that already accounted for by genotype. For males of hybrid strains, however, GR2 accounted for 55% of the variance in lifespan unattributable to genotype. Collectively, GENO and GR2 accounted for 85% of the obtained variation in lifespan for males of hybrid strains.

Finally, in a similar analysis, we examined the collective contributions of the measures of food efficiency and total food consumption to lifespan within each group. We found that EFF and FOOD failed to contribute significantly to the explainable variance in lifespan beyond that already accounted for by genotype.

TABLE IV

SUMMARY OF THE HIERARCHICAL REGRESSION OF LIFESPAN ON GENOTYPE AND GROWTH RATE ESTIMATES FOR MALE AND FEMALE MICE OF PARENTAL AND HYBRID STRAINS

Step	*Variable entered*	*R*	R^2	*Adjusted* R^2	*d.f.*	*F to enter*[a]	F[b]
Male inbred strains							
1	GENO	0.72	0.52	0.43	8/45	6.05***	
					8/45		6.05***
2	GR1	0.72	0.52	0.43	1/44	<1.0	
					9/44		5.37***
3	GR2	0.73	0.53	0.42	1/43	<1.0	
					10/43		4.78***
Female inbred strains							
1	GENO	0.67	0.47	0.39	8/45	5.01***	
					8/45		5.01***
2	GR1	0.69	0.47	0.36	1/44	<1.0	
					9/44		4.35***
3	GR2	0.69	0.47	0.35	1/43	<1.0	
					10/43		3.83***
Male hybrid strains							
1	GENO	0.66	0.43	0.33	5/30	4.51**	
					5/30		4.51**
2	GR1	0.69	0.47	0.36	1/29	2.91	
					6/29		4.33**
3	GR2	0.96	0.92	0.91	1/28	155.17***	
					7/28		48.99***
Female hybrid strains							
1	GENO	0.92	0.84	0.81	5/30	31.23***	
					5/30		31.23***
2	GR1	0.92	0.84	0.81	1/29	<1.0	
					6/29		25.50***
3	GR2	0.92	0.84	0.81	1/28	<1.0	
					7/28		21.11***

[a]The "F to enter" is a test of the significance of the increment in the proportion of variance accounted for by a given variable when entered next in the regression equation [27].
[b]The F ratio for the overall R at each step.
$^{**}p \leq 0.01$; $^{***}p \leq 0.001$.

DISCUSSION

The results of the present analysis support a morphogenetically based hypothesis of lifespan; however, the nature of the relationship between growth rate and lifespan was found to be sex-dependent. Among male mice of both inbred and hybrid strains, body weight and growth parameters were positively correlated to lifespan; whereas among females, the relationships were smaller and were generally negative. This contrast suggests that the genetic component of the hypothesized morphogenetic mechanism has

been oversimplified to the extent that predictions deduced from the hypothesis often produce contradictory results.

While there is no apparent contradiction in predicting a negative correlation between lifespan and growth rate and a positive correlation between lifespan and adult body weight, the data suggest that there is a contradiction. For example, sex is a genetic variable for which the predictions are often incompatible. Compared to males, female rodents are viewed generally as having slower growth rates and thus longer lifespans; however, they rarely achieve higher adult body weights [2, 15, 16, 21, 30]. Within heterogeneous groups of female rats, the negative correlations between growth rate and lifespan have been upheld, but no significant correlations between lifespan and peak body weight have been observed [16], although this relationship has been reported in male rats [16]. In the present study, female mice had slower growth rates compared to males, but there was no association of sex with lifespan. The lack of a sex differential in lifespan favoring females supports previous findings in mice [5, 15] but conflicts with the results of other mouse studies demonstrating a differential in favor of males [6, 31].

Hybridization is another variable for which predictions based on a morphogenetic hypothesis of lifespan often produce contradictions. As amply documented, hybridization is associated with increased longevity in laboratory rodents (see ref. 1 for review). This hybrid vigor was verified in the present study. Compared to parental strains, hybridization is also associated with higher adult body weights and higher growth rates [32–35]. In the present study, hybridization was associated with higher growth rates but only during the first 6 weeks after weaning.

Studies of obese mutations (*ob/ob*) also produce results that seem to contradict predictions based upon a morphogenetic hypothesis [7]. Compared to normal weight controls, obese mutations have shortened lifespans yet they achieve higher adult body weights at a faster rate. Within obese genotypes, however, the relationship between lifespan and growth rate is negative, while it is positive between lifespan and peak body weight [7].

Thus, there is little generality to predictions generated from the hypothesis in regard to inbred mouse strains. Part of the problem stems from possible methodological and mathematical discrepancies. For example, Storer's [26] failure to obtain significant correlations between lifespan and body weight may simply reflect his use of body weight data at 120 days of age, which falls far short of a representative adult body weight in mice. Sacher and Duffy [3] applied older age points (6–8 months and 24–34 months) and found significant positive correlations between body weight and age. Their analysis differed from the present one, however, in that they did not compute growth rates with which to compare to body weight, and they did not account for the prolongevity effects of hybridization; *i.e.* their regression analyses were conducted with progenitor and hybrid strains lumped together. Furthermore, like Storer, we examined correlations in both male and female mice. Sacher and Duffy examined correlations only among male strains. In addition, both previous analyses were based upon comparisons of individual strain means; whereas our analysis was based upon comparisons of sample means from individual strains. Therefore, we could examine the effects of genotype in our analysis.

In Goodrick's studies [7, 8], it is likely that the measure of the relationship between growth and lifespan was inappropriate, as suggested in subsequent analyses of his data on rats [24]. His growth rate measure was found to be more accurately a measure of growth duration (the age at which maximum body weight is attained) than it was a measure of rate of body weight increment during development in the rat. Representing a large portion of the lifespan in laboratory rodents, growth duration was, in fact, the most powerful predictor of lifespan both within and between groups of male and female rats [16, 24]. This parameter was also highly correlated to lifespan both within and between homogeneous strains of mice [7, 8]. Thus, it follows that the postulated morphogenetic mechanism controlling lifespan might not be reflected in the rate of body weight gain or in ultimate adult body weight attained; but rather it is best observed as the mechanism that maintains body weight increment. The prediction which follows, then, is that animals possessing the longest growth periods will have the longest lifespans.

While the empirical data generally support this relationship, there are problems in interpreting its specific nature. One problem is mathematical; that is, there is the likelihood that growth duration, which defines a major segment of the lifespan in these animals, would be positively correlated with length of life. As one increases, the other would also be expected to increase. A second question relates to the issue of morbidity, that is, the possibility that growth duration is determined by the onset of terminal illness. One could argue that a rodent will continue to gain body weight as long as it is healthy. This morbidity explanation has been supported in studies of rats [36, 37]. However, in a study of wild mice (*Mus musculus*), Duffy and Sacher [38] found no correlation between adult body weight and survival. Moreover, these investigators observed that the period of body weight decline in deer mice (*Peromyscus leucopus*) was so prolonged as to make the disease hypothesis untenable. This species, which is similar in adult body size to *Mus*, achieves its maximum adult body weight within the first 20% of its lifespan and steadily loses weight over the remaining 80%. Although arguing against a disease hypothesis, this observation also diminishes the importance of growth duration as a viable growth parameter for predicting lifespan. This is because the lifespan of *Peromyscus* is twice as long as that of *Mus*, but its peak body weight is attained in half the developmental time.

Constitutional variables of body weight and body weight gain and feeding efficiency were found to be correlated with lifespan in our sample of mice. Among hybrid males, growth rate during the first year of development was closely related to lifespan in a manner independent of genotype. This finding implies that environmental variables can enter the equation for predicting lifespan in addition to genetic variables. In other groups, however, genotype was the overriding factor in the relationship between growth and lifespan. As expected, genotype was highly related to all the variables that we examined. It was highly correlated with lifespan and with growth parameters, but the direction of the correlation was sex-dependent. Therefore, our findings indicate that growth parameters are genetically mediated but that the genetic component is expressed differentially in its relationship to lifespan according to sex. Our data suggest that, at the

very least, there are sex differences in the expression of this relationship, and other data on species differences suggest that other genetic factors may also mediate this relationship. At this stage, correlation certainly does not imply causation, and the previous inconsistencies suggest the difficulty of demonstrating a causal relationship. Indeed, such attempts at manipulating lifespan with growth hormones have been unsuccessful [39]. Finally, it can also be argued that inbred strains are not reasonable models for testing the hypothesis, because the forces of natural selection molding constitutional parameters to lifespan might have been altered considerably during the history of domestication and inbreeding.

In summary, the present analysis of intra-species correlation between lifespan and constitutional and growth variables supports the view that statistically significant relationships exist, but the meaning of these relationships is now further complicated by the lack of generalization across sexes. Furthermore, the nature of the conflict between a prediction of slow growth rate versus a high adult body weight remains to be resolved and thus detracts from the possibility for meaningful generalization. Consistent with Comfort's [13] assessment of Francis Bacon's early work on this hypothesis, we conclude that there is still insufficient data to support a general theory. While current interest remains in establishing the relationship between growth rate and lifespan [40], recent investigators have criticized the mathematical limitations of the correlational analysis of morphogenetic parameters and lifespan, and they have instead begun to re-emphasize the relationship of species-typical longevity to physiological and metabolic cycles [41, 42].

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