Special Article

Dietary habits and the prediction of life span of rats: a prospective test[1-3]

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ABSTRACT A multivariable statistical model for predicting the duration of life of rats permitted to select their own diets was evaluated prospectively. With information relating to pre-adult dietary habits and growth responses, the predicted length of life for an individual closely matched the observed life span; the average absolute error was 11%. This suggests that, even under normal feeding conditions, the diet/growth history is an important factor bearing on death rate. In general, an early adult death age is associated with a high food intake prior to adulthood particularly when coupled with a high efficiency of food utilization during the post-puberty period, a rapid growth rate and early attainment of mature weight. Deviations from this pattern serve to increase the duration of life of the individual. *Am J Clin Nutr* 1985;41:1332-1344.

KEY WORDS Longevity, mortality rate, aging, self-selection, growth, body weight

Introduction

The rate of aging and the duration of life reflect differences in genetic and environmental interactions among individuals of a species. The complex time-dependent and cumulative character of these interrelationships poses inordinate difficulties in explaining the mortality pattern of a population, let alone the longevity of any one individual. Nutrition, by modulating the changes that occur in a living system with passage of time, is recognized to be a significant environmental factor that can influence longevity. It is clearly evident that life span can be curtailed by malnutrition. The importance of diet as a life extending factor was established when McCay (1) demonstrated that the average life span of laboratory animals could be markedly increased by imposing a regimen of chronic underfeeding of a complete diet. Such regimens also reduced the frequency and/or delayed the occurrence of a number of age-related diseases (2-14) even when the composition of the diet was altered (3, 6-8).

While such studies are of experimental interest, inferences drawn may not be applicable in nonlaboratory environments. The stress of undernutrition, despite the lengthening of life span in the laboratory, is associated with functional and behavioral impairment and increased susceptibility to bacterial and parasitic diseases (15-19). At the other extreme, overnutrition is associated

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with a decreased capacity to resist some bacterial and viral diseases and with excess mortality from specific chronic degenerative disease processes (19–23). Dietary adequacy and moderation would thus appear to represent optimal conditions. Relatively little effort has been given to understanding the long-range consequences of intake of various dietary factors under normal feeding conditions, of interactions among dietary factors and of the variation in dietary practices that occur with age.

To resolve some of these problems, we have carried out a study of life-long duration that simulates natural conditions more closely than the conventional, arbitrarily fixed feeding regimen in that test animals are allowed to select among isocaloric diets that differ from each other only in their ratios of carbohydrate to protein. We have shown that when rats are allowed this freedom, dietary preference and growth vary from animal to animal and with age (24, 25), and that the duration of life can be correlated with differences in dietary practices and growth responses (26). Life span models for animals classified according to specific diseases or sites affected explained even higher proportions of the variance in longevity than did the "composite" model for which the proximate cause of death was not considered (27).

If the association between dietary practices and age at death revealed in these analyses is biologically meaningful, the non-disease-oriented models could serve as predictors of longevity. To evaluate these models as well as the concept that dietary habits of early life have long term consequences, another group of rats were permitted dietary choice with respect to protein:carbohydrate ratios throughout life. In this paper a correspondence is shown between the predicted and observed survival of an individual and age-specific mortality curve for the group. This permits us to conclude that even under normal feeding conditions, th diet/growth history is an important factor bearing on death rate.

Materials and methods

We attempted to duplicate the dietary and environmental conditions of our earlier study (model rats) (26), the results of which led to the empirically derived life span models. The earlier study began in 1967; this experiment, in different animal quarters, began in 1979. The National Research Council's guide for the care and use of laboratory animals was followed with the animals used in these experiments.

Rats, diet and environmental conditions

One hundred male non-inbred COBS rats, 21 days old, were obtained from Charles River Lab, Wilmington, MA (test rats). To maximize the genetic diversity among these rats, each was from a litter of different parentage. To reduce the possible effects of differences in dietary history during gestation and suckling, limits were set as to the parity of the dams (2nd or 3rd matings), litter size at birth and the number permitted to suckle, 10–13. A rat was not accepted if, during suckling, the number of siblings in a litter decreased to less than 10.

The rats were housed individually in suspended galvanized metal wire-bottom cages. Constant environmental conditions of the animal room were maintained throughout the course of the study: 73–74°F, 50–55% humidity, 13 changes of fresh air/h and a 12 h dark and 12 h light cycle. Fresh water was provided every 2nd day unless required more frequently.

Each rat was offered daily known amounts of 3 isocaloric diets differing only in their protein (vitamin-free test casein) and carbohydrate (sucrose) content (**Table 1**) (7). The protein-to-carbohydrate ratio ranged from

TABLE 1
Composition of purified diets

Constituents	D_{10}	D_{22}	D_{51}
	%	%	%
Casein*	10.0	22.0	51.0
Sucrose†	70.5	58.5	29.5
Corn oil‡	13.5	13.5	13.5
Salt mixture, USP XIII§	6.0	6.0	6.0
Vitamins‖ and trace elements¶			
Casein/Calorie ratio	1:11.1	1:5.1	1:2.2

* Vitamin-free test casein, 89% crude protein (nitrogen × 6.5).

† Domino Extra Fine Granulated Sugar, Amstar, New York.

‡ Mazola, Corn Products Co, New York.

§ Salt mixture, USp XIII No 2 composed of (%): $Ca(C_3H_5O_2)_2 \cdot 5H_2O$, 32.70; $Ca(H_2PO_4)_2$, 13.58; $FeC_6H_5O_7 \cdot 5H_2O$, 2.97; $MgSO_4$, 13.70; K_2HPO_4, 23.98; $NaH_2PO_4 \cdot 2H_2O$, 8.72; Nacl (iodized), 4.35.

‖ Vitamins (mg/kg of diet): thiamin hydrochloride, 3.3; riboflavin, 4.2; pyridoxine hydrochloride, 3.3; Ca pantothenate, 16.7; niacin NF-FCC (nicotinic acid, Roche), 16.7; folic acid (USP Parenteral, Lederle), 3.5; B_{12}, 0.05; menadione, 3.3; choline chloride, 4160; α-tocopherol, 160; oleum percomorphum, 133.3 (8,000 IU vitamin A and 1130 IU vitamin D_2).

¶ Trace elements (mg/kg of diet); $CuSO_4 \cdot 5H_2O$, 15; $ZnCl_2$, 15; $MnSO_4 \cdot 4H_2O$, 15; $CoCl_2 \cdot 6H_2O$, 0.15 (all minerals, USP reagent grade).

0.14 to 1.73, representing diets with a protein and carbohydrate content of 10 and 70.5%, 22 and 58.5%, and 51 and 29.5%. The levels of dietary fat (corn oil, 13.5%), minerals (6%), vitamins and trace elements were kept constant. The diets were supplied in separate wide mouth glass containers, each holding at least 5 gm more of the diet than the amount consumed. Thus each rat, by making appropriate selections in the amount taken from each container, regulated its protein intake apart from energy intake.

The quantity of each diet consumed, and thereby the dietary preference of each animal with respect to protein: carbohydrate ratios, was monitored daily. Corrections in the weight of unconsumed food were made for the amount of moisture absorbed from the air. From the intake information and body weight determinations, the following time-related sets of data were accumulated: the amount of food and calories consumed irrespective of the composition of the diet, the absolute intake of protein and carbohydrate, the proportion of protein in the composite diet selected, the intake of calories, protein and carbohydrate relative to body weight and the gross efficiency of food utilization (ie, gain in weight over a given period relative to the total amount of food consumed in that period). Expressions of growth response included: body weight at specified ages from which the absolute, the relative and the instantaneous relative growth rate (K) (28) were derived. From the growth curves, several age-independent parameters were also estimated: the interval required for a specific weight increment, interval to double body weight and the maximum body weight achieved. The latter was used as a measure of mature weight rather than the weight at an arbitrarily selected age in order to avoid the effects of terminal body weight loss that might be occurring in some animals. These data were also used to obtain a measure of metabolically effective body weight ($wt^{0.7}$) (28); they were also treated in accordance with a size dependent ecological constant ($wt^{0.17}$) that describes the relationship between average body weight and average life span among animals of different species (29).

Although the data required for testing the model could have been limited to specific age periods, the dietary information was, for purposes of completeness, collected on a daily basis for the first year and on alternate weeks for the remainder of life. Body weight data were collected weekly without interruption.

Health status and unusual behavioral characteristics were monitored daily. No therapeutic measures were taken except for our shortening of excessively long incisors, a result of lack of wearing on the semi-synthetic diets. Each rat was necropsied as soon as possible after death. In several cases, where it appeared that a moribund animal would not survive through the night, the individual was sacrificed and necropsied immediately. Every organ, whether grossly normal or diseased, was sampled for histopathologic study. All diagnoses were based on these observations.

Computations for prediction of life span of individual animals

The analyses used the life span as the dependent variable in a regression model, for which the cause of death was not considered. The statistical procedures used to derive these models have been described (26). Life span estimates were made on an individual animal basis. Correlation coefficients (r) were determined as a measure of the extent to which the predicted life spans among all individuals agreed with their observed life spans. Comparisons of the observed and predicted death age data were also made on a group basis by ranking the respective data according to age and constructing mortality tables from which age-specific mortality and survival curves were derived.

Results

Dietary practices. The average daily amount of food consumed and the average level of protein in the composite diet preferred by the test rats are shown in **Figure 1.** Unlike the relatively smooth patterns based on average values for the group, there was extensive diversity in dietary habits among individuals; for example, there was almost a two-fold difference between the amount of food consumed by the smallest and largest eaters. This difference remained or was even accentuated when the level of intake was expressed on a body weight basis. The extremes in the range for the proportion of protein in the diet selected by the rats differed by a factor of 3.5. Since there was no correlation between the amount of food consumed and the proportion of protein in the diet, the absolute protein intake was 4 to 5 times greater for some rats than for others. As was the case for rats of our earlier study, the absolute and relative amount of the 3 food mixtures consumed, and therefore of the dietary constituents, differed among test rats and with age to such an extent that no two rats had the same dietary histories. The age-specific data from the model rats and the test rats characterizing the dietary variables used in the analysis are given in a subsequent section.

Growth. The changes with age in the average body weight of the test rats are shown in Figure 1. The rates of growth, duration of the growth period and the weight attained at maturity also differed widely among the rats. During the exponential phase of growth, the most rapidly growing rats required only 45 days to reach 250 g while 66 days were needed for slowest growing rats to reach the same weight. With increasing age and weight, the individual growth pattern diverged even further so that as little as 33 days to as many

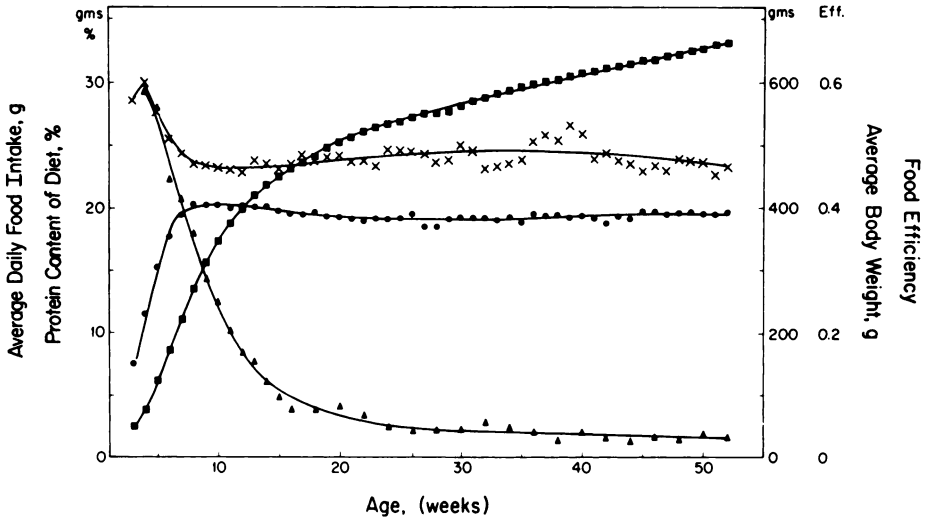

FIG 1. Dietary and growth characteristics during the first year of 100 rats permitted freedom of dietary choice throughout life; average weekly values. Food intake, ●; proportion of protein in the composite diet selected by the rats, ×; gross efficiency of food utilization, ▲; body weight, ■.

as 270 days were needed for the rats to gain an additional 250 g. Even though the efficiency of food utilization decreased with age (Fig 1), the variance for this parameter increased progressively so that among 5–7-month-old rats there was a sixteen-fold difference between the lowest and highest values. The duration of the interval over which body weight continued to be amassed varied from 315 to 889 days. The average maximum weight attained was 805 g (ranging from 559 to 1180 g), while the average maximum weight attained by the model rats was 890 g (ranging from 572 to 1320 g) ($p < 0.01$).

Diseases. Among the 100 test rats, there was one accidental death. For two animals, no pathologic lesion was found that might have been responsible for the proximate cause of death. For each of the remaining 97 rats, a specific disease or combination of organic lesions was assigned as contributing to death. Sixty-six percent of these rats had tumors; among these, 47% had 2, 3 or 4 primary tumors differing in tissue origin, site or type (in the retrospective experiment, 67% of rats developed tumors). The kidney, heart and prostate gland were the most common sites for the non-neoplastic age-related diseases. Glomerulonephrosis in varying degrees of severity was found in 72% of the rats; 37% had myocardial fibrosis or areas of myocardial calcification and 28% had prostatitis.

Mortality. Age at death had a nearly symmetric distribution with a range of 406 to 990 d (**Fig 2**). The first natural death was at 436 d. The age-specific mortality rate increased linearly with age on a log-log plot. The median life span (704 d) and the estimated 50% survival age (~700 d) were in close agreement with the mean value, 711 ± 121 d ($\bar{x} \pm SD$).

The death by age frequency curve for the rats was displaced to later ages when compared to the distribution curve for the model rats (Fig 2); the average life span of the test rats was 12.5% greater than that of the model rats.

Prediction of life span. The first model tested was a 7 variable regression equation that explained nearly 50% of the variance in the life span of rats in the earlier study (26). The variables included in this model were: *1*) the absolute level of protein intake, *2*) the proportion of protein in the diet, *3*) the efficiency with which the amount of food consumed was directed to growth, *4*, *5*) the body weight at two age periods, *6*) the time required for a specified weight increment and *7*) the age when a specified weight was reached. When the coefficients of this equa-

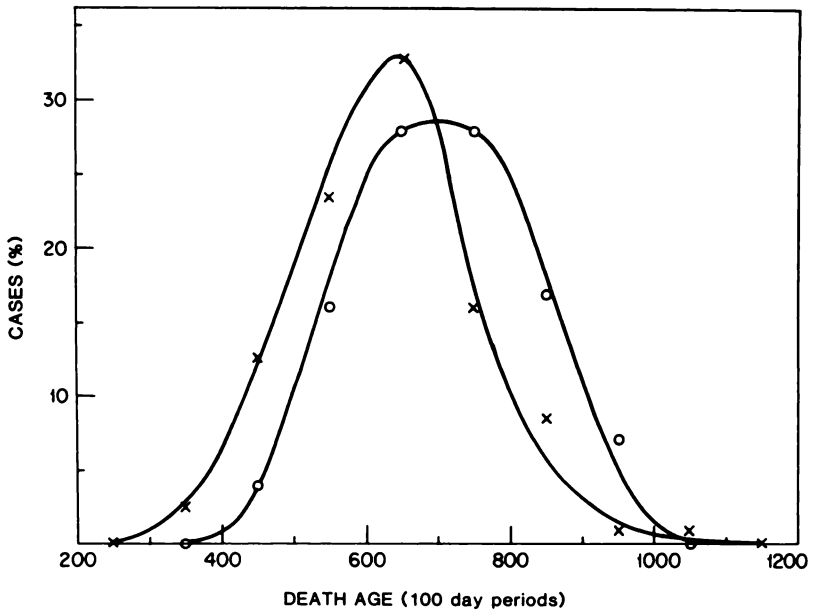

FIG 2. Mortality distribution in 100-day age periods of rats permitted freedom of dietary choice; observed data. Rats of the current prospective study, O; rats of the retrospective experiment, ×.

tion were applied to the appropriate data from the test rats, the average of the predicted life span for the group (720 days) was in close agreement with their actual average life span (711 days). On an individual basis, however, there was no significant correlation between predicted and observed life spans ($r = 0.16$); the average absolute error between the estimated and actual life span exceeded 17%.

Upon reexamining this model, it was found that although the criterion of statistical significance of each variable in the complex had been satisfied, colinearity between two of the factors was present. Thus, prior to testing other models, we found it necessary to reanalyze the data from the model rats. This provided an opportunity to introduce mature weight into the analysis of the model rats. This variable was added because of its importance in several non-colinear multivariable death-age models for animals classed according to specific types of tumors found at death and because of the strong correlation reported between the average body weight and average life span among animals of different species.

In the earlier study, mature weight did not correlate significantly with life span. In combination with other variables, however, it was a significant factor. The best of the new series of models included this variable and explained an even higher proportion of the variance (55%) in life span of the model rats. Aside from the inclusion of mature weight, this model differs from the earlier version principally in that the proportion of protein in the diet is excluded.

When the coefficients in this regression equation were applied to the data from the test rats, the average estimated life span was within 0.5% of the average observed life span. While the estimated life spans on an individual basis correlated significantly with the actual life spans ($r = .24$, $p < 0.01$). The average absolute error was still rather large (14.5%).

The model which best fits the retrospective data, however, may not be best for purposes of prediction. This could occur if some variables achieved statistical significance by explaining the life span of a small subset of the animals. Such a model, therefore, may contain more variables than the ones which are of fundamental importance for characterizing the life spans of animals of other groups. This appeared to be the case. For example,

some models comprised of 5 variables increased the extent to which predicted values correlated with actual values. A still further reduction in the number of variables resulted in a marked improvement in accuracy of prediction.

The four variable model that best fit the data from the model rats yielded, for those rats, a correlation coefficient between the observed and estimated life spans of 0.57. When this model was used to predict the life span for each of the test rats, the correlation coefficient with the actual life span was 0.55. This model included the following variables: (X_1) the age when a specified weight is reached (approximately the age at puberty), (X_2) the amount of food consumed during the post-puberty period, (X_3) the efficiency of food utilization prior to adulthood and (X_4) the mature weight. The coefficients for each of these variables in the regression equation are shown in Table 1. The specific age periods for these variables, a description of the data from which this model was derived and the data used to make the predictions are also shown in **Table 2.** Deletion of any one of the 4 factors from this combination led either to a nonsignificant model or to models which when tested prospectively gave rise to lower levels of correlation between predicted and observed death ages and to higher errors in the predictions. The same applies to any other combination of three variables.

With the above 4 variable regression equation, the average absolute error between the individually predicted and observed life spans was 11.3%. The accuracy in the predictions was better than 95% for more than 25% of the animals, and better than 90% for more than half the animals and for only 16% of the rats was it less than 80% (**Table 3**). An error of 10% represents a difference of less than 50 days for the shortest lived rats; and approximately 90 days for the longest lived rats. The frequency distribution in the errors among the model rats is nearly identical to the prediction errors obtained when the model was applied to the test rats.

Unlike the more complex models, information on the proportion of protein of the diet selected and/or the absolute intake of protein is not required in this 4 variable model. The absence of such factors does not necessarily imply that they are of little importance. The effects of the level and interrelationships among all essential dietary con-

TABLE 2
Multivariable linear regression equation for predicting life span

Variables	Data values mean ± SD (range)		Coefficients of regression equation*		t statistic of coefficients‡
	Model rats	Test rats	Normal	Standardized†	
X_1 Age at 250 g body wt, d	55.1 ± 6.72 (44–95)	53.6 ± 3.61 (45–66)	3.99	0.214	2.41
X_2 Av. daily food intake, g (99–147 d)	21.0 ± 1.90 (15.5–26.7)	19.7 ± 1.84 (14.9–25.2)	−29.60	−0.448	−5.22
X_3 Av. Gross food efficiency, g (148–196 d)	0.064 ± 0.020 (0.003–0.138)	0.039 ± 0.015 (0.005–0.080)	−2113.8	−0.337	−3.65
X_4 Mature body wt., g	890.7 ± 145.1 (572–1320)	805.5 ± 129.2 (559–1180)	0.387	0.448	4.46
Intercept			823.3	0	

* Derived from model rat data (26). Expressed in the form of a linear multiple regression equation, $Y = a + b_1X_1 \cdots b_4X_4$, where Y = predicted life span in days; b, the coefficient of the independent variable, and X, the data values of the appropriate variables for the individual. Positive values contribute to an increase in the predicted duration of life; negative values contribute to a reduction in the predicted life span.

† Standardized coefficients derived from model rat data after normalizing the values of the random variables: $\frac{x - \bar{x}}{SD}$. The higher the standardized coefficient, irrespective of sign, the greater the contribution of the variable to the predicted value (Y). The standardized coefficients indicate the extent of change in the predicted life span associated with a change of 1 SD in the value of the independent variable.

‡ All t values significant ($p < 0.01$); F statistic for multiple regression equation, 13.5 ($p < 0.00001$).

TABLE 3
Accuracy of life span predictions

Prediction accuracy, %*	Number cases
<70	3
70–74	3
75–79	10
80–84	13
85–89	18
90–94	26
>95	26

* Accuracy computed as:

$$1 - \left(\frac{|\text{Predicted life span, d} - \text{actual life span, d}|}{\text{actual life span, d}}\right);$$

expressed as %.

stituents, including protein, are incorporated indirectly in another parameter—the efficiency factor (30–32). By including the growth promoting or limiting effects attributable to the unique composition of the diet selected by the genetically diverse animals, the efficiency variable takes on greater significance than expected from an expression of the age-dependent relationship between food intake and body weight.

The model, however, has several deficiencies. The average of the predicted life span of the test rats was 4% less than that of the average actual life span. Except for the very shortest-lived rats, there was an overall tendency for the predictions to underestimate death ages (**Fig 3**). We considered the possibility that this might be due to the constant in the model. To obtain a model without this constant, it was necessary to normalize the data from the model rats and to calculate the standardized coefficients for the 4 variables. The values of the coefficients of this equation also serve to indicate their relative importance (Table 2). As a result of these transformations and appropriate normalization of the data from the test rats, there was no change in the slope in the regression between the actual and predicted values but there was a displacement of the regression line of approximately 15 days. This suggested a small improvement in the predictions (Fig 3). The average absolute error was now 11.2% but the life spans of the shortest-lived rats were still overestimated.

Another possibility that might account for some of the deviations was in the use of actual body weight data. Transforming mature body weight data was performed to yield: *1*) a measure of the metabolically effective body weight ($wt^{0.7}$) and *2*) a size dependent ecological constant ($wt^{0.17}$) for longevity. The coefficients obtained from the models in which these data replaced the absolute weight data were applied to the appropriately modified data of the test rats. It was found that absolute weight values provided predictions as good as, if not better, than the transformed values.

Conventional actuarial procedures were also used to determine whether it was possible to construct the age-specific mortality rate and survival curves on the basis of predicted values. The normal coefficients of the model were used for this purpose. The results shown in **Figures 4 and 5** indicate that the predicted curves approximate those based on observed life span data. They also reveal the high degree of accuracy of the predictions for the

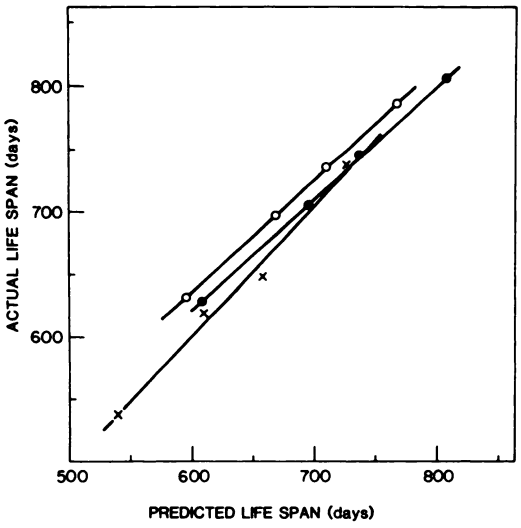

FIG 3. Comparison of actual death age with death age predicted prospectively from the application of the normal coefficients of the regression equation given in Table 1, O. Prediction computed from standardized coefficients given in Table 1, ●. Actual and estimated life spans of rats of the retrospective experiment that provided the mathematical model used in the prospective study shown for comparison purposes, ×. In each curve, the 4 points represent the average of predicted and actual values for nearly equal numbers of rats; prospective experiment, total n = 99; retrospective experiment, total n = 119.

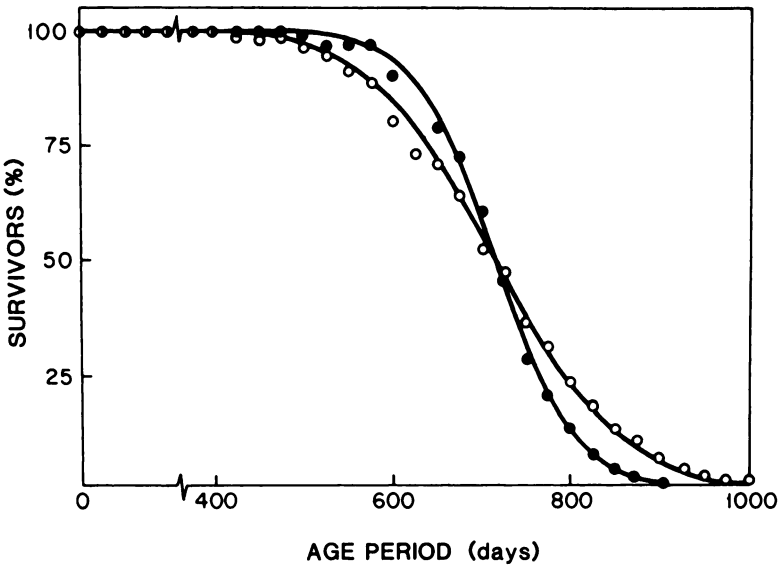

FIG 4. Predicted survival curve of rats, ●, actual survival curve of rats, O.

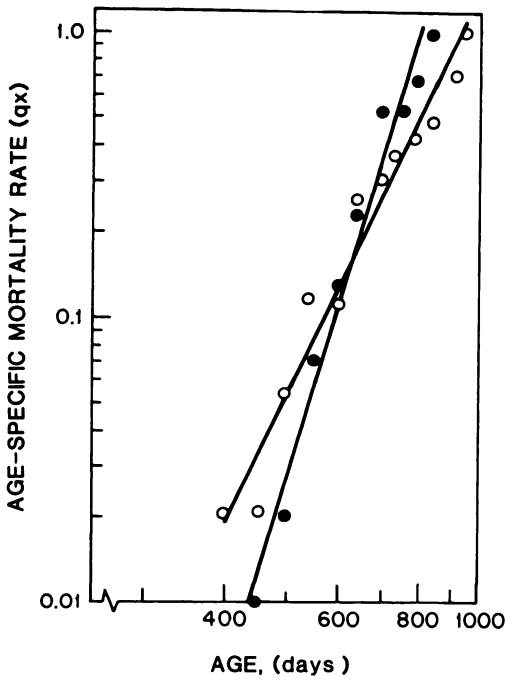

FIG 5. Complete age specific mortality rates at successive 50-day age periods. Actual rates based on observed data, O; predicted rates based on individual death age predictions, ●. Mortality rates equal the number of rats dying or predicted to die within a period against the number of rats alive or predicted to be alive in the total group entering that period.

intermediate lived rats, the overestimation of the predictions for the shortest-lived rats and the underestimations for the longest-lived rats; the average errors at the very extremes being less than 100 days.

Discussion

We have carried out a controlled prospective study designed to relate variations in certain feeding preferences to the survival of laboratory rats maintained on defined diets. The basal diet selected for these experiments was that used in our previous studies (7). This synthetic diet contains levels of Cu, Zn, and Mn that are generally lower than those recommended by the National Research Council. In addition, biotin was not added to the diet. Although under normal feeding conditions, biotin is supplied through bacterial synthesis in the gut, rodents must reingest their feces in order to benefit from this supply. Since rats in these studies were maintained on wire surfaces, coprophagia may have been somewhat restricted, raising the possibility of a mild biotin deficiency. No gross or microscopic signs of biotin or mineral deficiency were observed.

In spite of the possible nutritional deficien-

cies indicated or other unknown nutritional deficiencies in the basal diet, we elected to continue the present studies using the original basal diet in order to preserve the effects of the variable protein:carbohydrate ratio on growth and longevity that we have previously described. Perhaps a basal diet that differs in composition from the one we are using would show a different effect of protein:carbohydrate ratio on growth and longevity, perhaps not. Such effects of varying the basal diet would have to be demonstrated by additional studies; nevertheless, we believe that the conclusions drawn concerning the consequences of variations in feeding preferences that result in differing intakes of protein, carbohydrate, and total calories, if taken in the context of this particular diet, are valid.

We have established that it is possible to predict with reasonable accuracy the length of life of an individual and the survival curve of the group, solely on the basis of information relating to diet and growth. Therefore the factors used for these predictions do, in fact, influence the aging process, either directly or indirectly, and/or are manifestations of the rate of aging.

Our work differs from that of others in this field in a number of ways. Under the self-selection method of feeding, the diet chosen is presumably of physiological significance to the individual, and individual variation in dietary and growth behavior can be expressed. The effects of imposed deficiencies or excesses of one or more dietary components are avoided. With an unvarying regimen it may not be easy to distinguish the benefits accruing from a diet at one stage of life from the detrimental effects of the same diet at a later age. With the self-selection regimen, on the other hand, it was possible to define the temporal sequence when each essential factor contributed significant life-shortening and -extending information, thereby demonstrating how differences in life span can be accounted for by differences in the dietary practices and growth behavior of the animals. With conventional fixed diet studies, inferences are drawn from a series of isolated relationships regarding the importance of diet and/or body weight on life span on a group basis. We used the data from individual rats permitted dietary self-selection in the retrospective experiment to analyze the interactive effects among variables. Our statistical model derived through these analyses can be used to predict the longevity of an individual. By demonstrating the accuracy of these predictions, we have also supported our premise that dietary practices and growth responses relatively early in life have long-lasting effects on life span.

In general, long life was associated with a combination of specific factors that describe or contribute to a low rate of growth maintained over a prolonged period so that the normal range of mature weight is still reached. Deviations from this pattern serve to shorten life span. Thus, a high intake of a complete diet prior to adulthood, particularly if coupled with a high efficiency of food utilization during the post-puberty period, contributing to a rapid growth rate and early attainment of mature weight, will in most cases, decrease the span of life.

Our primary conclusion is that even under nonstressful dietary conditions, factors that modulate the rate and duration of growth are linked with life span. This is compatible with observations made with other experimental approaches. In laboratory rodents, overnutrition of genetic or induced origin (33–35) and high efficiency of food utilization resulting in early maturity and long-standing obesity (36–38) are associated with a short life span (30, 39, 40). In contrast, undernutrition during the developmental period increases the duration of life for a variety of animal forms (41). In a laboratory setting, chronic underfeeding of an adequate diet to rats, mice and hamsters, immediately after weaning, is associated with a life expectancy far in excess of that obtained with animals fed ad libitum (1–3, 5, 10, 11, 42–47). Animals whose food intake is restricted are also less efficient in converting the food consumed into body mass, which contributes further to a reduced growth rate and a depressed mature weight (48, 49). However, because of a high infant mortality (50) and developmental impairment of the endocrine, immunological and central nervous systems (15–18) that accompany severe growth stunting, it is questionable that animals would experience an extended survival in an open environment.

The inverse correlation between the average

mature weight and life expectancy among groups of chronically dietary restricted animals is opposite to that found for animals permitted dietary self-selection. It also differs from the positive correlation between body weight and life span among animals of 150 species ranging from daphnia to elephants (29, 51–54). Even within a dietary group, the heavier animals are more likely to be among the longer lived (55–57). The results of our present study appear to resolve this discrepancy. With unvarying fixed regimens of restriction, the conditions that depress growth early in life persist into later life to depress mature weight as well. As a result, there are significant simple inverse correlations between growth rate and life span and between mature weight and life span. Among animals free to modify their dietary practices with age, the pattern differs. Animals may grow rapidly and reach their mature weight relatively early in life or they may grow at a slower rate and remain small at maturity or attain weights that approach those of the faster growing rats but do so at an older age. Thus the correlation between body weight early in life and life span may differ in direction from that obtained for body weight later in life or, as in the present study, mature weights of long-lived rats do not differ significantly, on a simple correlation basis, from those of the short-lived rats.

Equally important in explaining the different conclusions reached from restricted and normal feeding studies is the relative contribution of early and mid-life factors. In accordance with our findings, the life-prolonging sum effect of the combination of low food intake, low efficiency and low growth rate, as would be the case with imposed dietary restriction would predominate over any life-shortening effect stemming from low mature weights. For example, a rat, whose intake of food and efficiency of food utilization was lower than that of another, (each by one SD) and which required somewhat longer (by one SD) to reach a specified weight early in life could be expected to be longer lived by more than 100 days, if it attained the same mature weight. If, however, the mature weight of the rat was lower by 100 g (0.8 SD) from that of the other, it would still be longer lived because the predicted life span would be reduced by only 38 days. Thus the relationship between mature weight and life span would seem to be dependent upon the age when a dietary regimen is begun and its duration, and the response of the individual to the dietary conditions (58–60). A reasonable conjecture is that greatly extended life spans could be obtained under experimental conditions if, instead of limiting the amount of food throughout life, the period of underfeeding and consequent growth depression was confined to the pre-adult phase of life.

Stuchlikova et al (46) examined the life span modifying effects of restriction begun at different stages of life. They reported that rats, mice and hamsters, underfed for the first year postweaning and then permitted to feed ad libitum for the remainder of life, became obese but were even longer lived than animals that were restricted throughout life or during the 2nd half of life only. McCay (61) and Beauchene (62) also showed that nutritional rehabilitation after extended periods of growth retardation also led to an increased life span of the survivors over ad libitum fed rats. The period of growth retardation during early life need not be overly long to obtain a long-lasting beneficial effect on life span. Dietary induced growth depression during the first 7 weeks postweaning followed by ad libitum feeding for the remainder of life also led to a significant improvement in life expectancy and a decided reduction in the frequency of a number of age-related diseases (63). Nolen (10) who restricted his rats for 12 weeks early in life and then fed them ad libitum, found that the mature animals were heavier in weight and had a longer mean life span than rats fed ad libitum throughout life.

Conversely, a regimen of underfeeding, which when begun at weaning age increases life expectancy over ad libitum fed animals by approximately 50% shortens life span by approximately 50% if begun instead at 300 days of age (58). Other workers (64–66) also found that food restriction begun at middle age shortened life span or did not result in a further increase in life span. Even a delay of 12 weeks before a regimen of mild restriction was begun results in shorter lived animals compared to those that were restricted to the same degree throughout postweaning life (10).

These data from dietary intervention studies agree with our findings and lend support to the hypothesis that early nutritional experiences and growth characteristics have a strong influence on life span. They do not, however, exlude the possibility that dietary intervention later in life can also have beneficial effects. The adjustments in dietary composition necessary as well as the degree and method of restriction are critically dependent on the age of the animal (58, 59, 67). However, the extent of increase in life expectancy is less than that of animals maintained on that regimen throughout the greater part of life. Moreover, the frequency of some tumors among the late restricted animals are either unchanged from that of the ad libitum fed animals or not decreased to the same extent as when the restriction was begun at earlier ages. The differential effects of early and midlife dietary intervention on disease frequency (45, 67), the specificity of the variables in the models that explain the variance in mortality of animals dying with different diseases (27), and the difference in body composition following restriction and following nutritional rehabilitation (10, 30, 68) suggest that the mechanism whereby restriction begun at different periods of life influences the rate of aging is not identical.

It is not known whether the metabolic response of an organism to an imposed unvarying diet differs from the changes that occur in animals permitted to select and change their dietary intake with age. When the diet is provided by the investigator, it can be considered as an external or environmental factor, and as a consequence, the metabolic efficiency and growth characteristics are expressions of the interaction of the genetic background of the subjects and the quantity and quality of the diet consumed. In the case where animals select among different diets, each of the factors in our model, ie, the amount of energy consumed, the efficiency of food utilization, extent of early growth and mature body weight may be to a large extent genetically determined. There are also intrastrain differences in the efficiency of energy utilization and in the neuroendocrine regulatory mechanism of food intake (69). Selective breeding for rapid early growth is associated with significantly higher levels of food intake, energy utilization, maximum weights at earlier ages and markedly shortened life spans (30, 38–40, 70–72). The converse is also the case when selective breeding is based on slow growth rates (39, 40, 55).

In the light of these observations, the question is raised as to the extent to which the results reported here were determined by heredity or the dietary environment. Nevertheless, there is a commonality of the dietary and growth-related variables associated with duration of life that applies to animals maintained on a self-selection regimen, on an imposed dietary regimen and between animals of different strains on the same regimen. Thus, even without mature weight information, there are readily measurable pre-adult parameters (food intake, efficiency of food utilization and rapidity of growth) that can be used to evaluate the expected duration of life of an individual. Although, in a natural environment, an indeterminate number of factors have an impact on life span and those relating to diet and growth may not be as important as others, the laboratory studies do reveal the presence of a mechanism centering on diet and growth that can be modified to help increase for some, but not all individuals, the expected length of life.

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