Journal of Gerontology
1986, Vol. 41, No. 1, 13-19



# Effect of Age of Initiation of Feed Restriction on Growth, Body Composition, and Longevity of Rats[1]

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**Male Wistar rats were maintained on four dietary regimens: fed ad libitum throughout life (A); fed intermittently either during the first year of life and ad libitum thereafter (RA) or vice versa (AR); and fed intermittently throughout life (R). Low body weights, low amounts of body components (protein, fat, moisture, and ash), and long life spans were observed in R. AR and RA lost or gained body weight, respectively, after dietary transfer and lived longer than A. Maximum body weight and the age at which it was attained were correlated positively with life span in A. Predicted mature body weight was correlated negatively with life span in R. RA and AR differed in growth and body composition, but their life spans were similar and intermediate to those of A and R. Increases in life span were obtained by intermittent feeding during all or part of the life span, but growth and body composition data did not consistently explain the mechanism of this effect.**

**Key Words: Dietary restriction, Life span, Aging, Growth, Lean body mass, Adipose mass**

DIETARY restriction may be the most effective method of extending the life span of laboratory animals (Weindruch et al., 1982). Early studies with rats (McCay et al., 1935) led to the hypothesis that slowing the rate of growth was necessary to increase longevity. The increases in the life spans of rats in which feed restriction was initiated at 6 (Masoro, 1984), 12 (Stuchlíková et al., 1975), or 18 (Goodrick et al., 1983) months of age indicate an effect of restriction on longevity independent of its effect on growth. Severe dietary restriction (40% to 50%) imposed after growth cessation, however, has been reported to have no effect on life span (Everitt et al., 1980) or to decrease it (Barrows & Roeder, 1965).

The relationship between growth and life span may be reflected by changes in body composition. Alterations in lean and adipose mass with age differ according to dietary treatment (Bertrand et al., 1980). Although it has been traditionally believed that increased body fat content accompanies aging, not all studies support this conclusion (Bertrand et al., 1980; Lesser et al., 1973). It has been suggested (Goodrick, 1978) that increased growth duration, rather than the reduction in body weight, per se, is responsible for the prolonged life span of food restricted animals. In fact, Bertrand et al. (1980) found no relationship between body adipose mass and length of life in food restricted Fischer 344 rats. The recent reports of life span extension in response to dietary restriction initiated after growth cessation add yet another factor to be considered. We have, therefore, investigated the relationships among growth, body composition, and longevity of rats in which feed restriction was initiated at weaning or at 12 months of age.

## Materials and Methods

*Animals and dietary treatments.* — Thirty-day old Wistar outbred male rats were assigned randomly to experimental groups as shown in Table 1. The animals were housed 5 per wire mesh cage in a conventional facility maintained at 23 ± 2 °C with a 12 hour light/12 hour dark cycle. The animals were fed ground lab chow (Wayne Lab Blox, Allied Mills, Specialty Feeds Department, Chicago) which contained 24.5% protein, 50.2% carbohydrate, 4.1% fat, 4.5% fiber, and vitamins and minerals in amounts to meet requirements for rats

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Table 1. Animal Groups and Dietary Treatments

| Group designation | Number of animals per group | | Feeding regimen | |
|---|---|---|---|---|
| | Biochemical | Longevity | Until 12 months | After 12 months |
| Young | | | | |
| Ad libitum (AY) | 11[a] | — | ad libitum | — |
| Restricted (R) | 11[a] | — | restricted | — |
| Old | | | | |
| Ad libitum (A) | 10[b] | 45 | ad libitum | ad libitum |
| Restricted (R) | 11[b] | 45 | restricted | restricted |
| Ad libitum/restricted (AR) | 11[b] | 45 | ad libitum | restricted |
| Restricted/ad libitum (RA) | 11[b] | 45 | restricted | ad libitum |

[a]Sacrificed at age 12 months.
[b]Sacrificed at age 24 months.

(National Academy of Sciences, 1972) according to the manufacturer. Feed restriction was accomplished by making feed available only from 5:00 p.m. to 8:00 a.m. on alternate days. Feed intake, corrected for spillage, was measured biweekly until 4 months of age and monthly thereafter. Water was provided ad libitum. Biochemical animals were sacrificed at 12 or 24 months of age. Longevity animals were maintained on identical dietary regimens and allowed to live their natural lifespans. Cages were checked for deaths twice daily and gross autopsies were performed to determine the extent of lung and kidney disease and visible tumors. Monitoring for specific pathogens was not performed. The rats were obtained as weanling animals from National Research Laboratories, Creve Coeur, MO. They were born May 1, 1972; the last survivor died May 18, 1976.

*Growth parameters and body composition.* — An exponential growth curve (Brody, 1964) was used to calculate relative growth rate and to predict mature body weight of the longevity animals. Body weights measured 16 times during the first year of life were used in the equation: $W = A - Be^{-kt}$, where $W$ = body weight in grams at age $t$ in weeks; $A$ = the predicted mature body weight in grams; B = an integration constant; e = base of natural logarithms; and $k$ = relative growth rate with respect to the growth yet to be made. At sacrifice, rats were stunned by a blow to the head, decapitated, and their gastrointestinal contents were removed. Body constituents (water, protein, fat, and ash) were quantified using a modification of the method of Hartsook and Hershberger (1963) and were calculated in both absolute and relative amounts. A modification of Duncan's multiple range test (Kramer, 1956) was used to identify statistical differences ($p < .05$) among means. Correlation coefficients (Pearson's $r$) between test responses were calculated as described in Steele and Torrie (1960).

## RESULTS

*Feed consumption, growth parameters, and body weights.* — At 2.5 and 12 months of age mean feed consumption of restricted rats was 55% and 67%, respectively, of that eaten by rats fed ad libitum. The latter level of consumption was maintained approximately by R rats throughout the second year of life. At 2 years of age AR and RA rats ate 75% and 90%, respectively, of the feed consumed by A animals.

As shown in Table 2, relative growth rates ($k$ values) and predicted mature body weights of rats restricted during the first year of life (R and RA) were significantly less than those of rats fed ad libitum during the first year (A and AR). Actual maximum body weight was higher for A than R rats, although the age at which their actual maximum body weight was first attained did not differ. AR rats attained a higher maximum body weight than RA rats; maximum body weights of both groups were intermediate with those of R and A animals. Actual maximum body weights exceeded predicted body weights by 11.4%, 7.6%, 3.0%, and 37.4% for A, R, AR, and RA groups, respectively.

*Body composition.* — Feed restricted rats of both young and old groups had significantly smaller amounts of body fat, protein, ash and moisture than corresponding groups fed ad libitum (see Table 3). During the second year of life R animals laid down more than three times as much protein and twice as

much ash as A animals. A rats, however, deposited five times more fat than R rats. Absolute amounts of body components of AR and RA were similar except for fat; RA had almost twice as much body fat as AR animals at 2 years of age.

During the first year of life, feed restriction had no effect on relative body composition (Table 4). At 2 years of age, R rats had higher percentages of body protein and ash and lower percentages of fat than A rats. The relative body composition of AR

Table 2. Influence of Dietary Restriction on Growth Curve Parameters and Maximum Body Weights of Longevity Rats

| Group | Relative growth rate[a] ($k$ values) | Predicted mature body weight[b] (grams) | Actual maximum body weight (grams) | Age maximum body weight attained[c] (weeks) |
|---|---|---|---|---|
| Ad libitum | 0.116 ± 0.003$^{A}$ | 499.9 ± 8.9$^{A}$ | 557.1 ± 10.6$^{A}$ | 91.9 ± 3.8$^{B}$ |
| Restricted | 0.097 ± 0.003$^{B}$ | 358.8 ± 5.1$^{B}$ | 386.2 ± 5.4$^{D}$ | 89.7 ± 3.5$^{B}$ |
| Ad libitum/restricted | 0.114 ± 0.003$^{A}$ | 515.9 ± 8.0$^{A}$ | 531.2 ± 7.7$^{B}$ | 53.8 ± 1.8$^{C}$ |
| Restricted/ad libitum | 0.096 ± 0.003$^{B}$ | 356.1 ± 6.4$^{B}$ | 489.0 ± 7.9$^{C}$ | 115.0 ± 1.7$^{A}$ |

*Note.* Values are means plus or minus the standard errors of the means. Means in a column not sharing a common superscript are significantly different from each other ($p < .05$).

[a]Relative growth rate = $k$ in Brody (1964) equation.

[b]Predicted mature body weight = $A$ in Brody (1964) equation.

[c]Youngest age at which maximum body weight attained.

Table 3. Effect of Feed Restriction and Age on Absolute Amounts of Body Components of Male Rats

| Group | Body weight (grams) | Moisture (grams) | Protein (grams) | Fat (grams) | Ash (grams) |
|---|---|---|---|---|---|
| 1-year old | | | | | |
| Ad libitum | 473 ± 13$^{B}$ | 276 ± 5$^{B}$ | 97.4 ± 2.9$^{A}$ | 90.7 ± 6.4$^{B,C}$ | 15.1 ± 0.9$^{A}$ |
| Restricted | 290 ± 9$^{E}$ | 176 ± 7$^{C}$ | 59.9 ± 2.2$^{C}$ | 46.1 ± 2.9$^{D}$ | 8.7 ± 0.6$^{C}$ |
| 2-years old | | | | | |
| Ad libitum | 531 ± 13$^{A}$ | 305 ± 7$^{A}$ | 100.0 ± 2.9$^{A}$ | 123.9 ± 11.1$^{A}$ | 17.0 ± 0.9$^{A}$ |
| Restricted | 332 ± 11$^{D}$ | 201 ± 6$^{D}$ | 68.7 ± 2.3$^{D}$ | 52.6 ± 4.8$^{D}$ | 12.4 ± 0.5$^{B}$ |
| Ad libitum/restricted | 413 ± 8$^{C}$ | 247 ± 5$^{C}$ | 85.6 ± 1.8$^{B}$ | 67.5 ± 4.1$^{C,D}$ | 15.9 ± 0.8$^{A}$ |
| Restricted/ad libitum | 466 ± 12$^{B}$ | 250 ± 6$^{C}$ | 91.0 ± 2.7$^{A,B}$ | 117.0 ± 8.8$^{A,B}$ | 14.9 ± 0.8$^{A}$ |

*Note.* Values are means plus or minus the standard errors of the means. Means in a column not sharing a common superscript are significantly different from each other ($p < .05$).

Table 4. Effect of Feed Restriction and Age on Relative Body Composition of Male Rats

| Group | Moisture (%) | Protein (%) | Fat (%) | Ash (%) |
|---|---|---|---|---|
| 1-year old | | | | |
| Ad libitum | 58.6 ± 0.8$^{A}$ | 20.6 ± 0.2$^{A}$ | 19.0 ± 0.8$^{B,C}$ | 3.2 ± 0.2$^{B}$ |
| Restricted | 60.8 ± 0.8$^{A}$ | 20.7 ± 0.3$^{A}$ | 15.9 ± 0.8$^{C}$ | 3.0 ± 0.2$^{B}$ |
| 2-years old | | | | |
| Ad libitum | 57.7 ± 1.9$^{A,B}$ | 18.8 ± 0.4$^{B}$ | 23.2 ± 1.9$^{A,B}$ | 3.2 ± 0.2$^{B}$ |
| Restricted | 60.8 ± 0.9$^{A}$ | 20.7 ± 0.2$^{A}$ | 15.6 ± 1.1$^{C}$ | 3.8 ± 0.1$^{A}$ |
| Ad libitum/restricted | 59.9 ± 0.6$^{A}$ | 20.7 ± 0.2$^{A}$ | 16.3 ± 0.8$^{C}$ | 3.8 ± 0.2$^{A}$ |
| Restricted/ad libitum | 53.7 ± 1.3$^{B}$ | 19.5 ± 0.4$^{A,B}$ | 24.9 ± 1.6$^{A}$ | 3.2 ± 0.1$^{B}$ |

*Note.* Values are means plus or minus the standard errors of the means. Means in a column not sharing a common superscript are significantly different from each other ($p < .05$).

rats was similar to that of R animals at 2 years of age. Both groups fed ad libitum during the second year (A and RA) had lower relative amounts of protein, ash, and moisture, which were associated with greater percentages of body fat. Excluding higher proportions of ash, relative body compositions of animals restricted during their second year of life (R and AR) were not significantly different from those of young rats (AY and RY).

*Life span.* — The life span of R rats was longer than those of other groups (see Figure 1 and Table 5). The life spans of transferred groups (AR and RA) were not different from each other but were greater than that of group A. Similarly, the life span of animals that lived the longest (maximum life span) in each dietary group were greatest for R rats. Maximum life spans of AR and RA groups again did not differ but were greater than that of A rats.

Feed restriction did not result in excessive early mortality, as evidenced by the 97% survival rate at 52 weeks of age for R and RA rats. The incidence of lung disease at time of death in all longevity animals was less than 14%; kidney lesions and tumors were present in 23% and 37% of the animals, respectively. AR and RA rats tended to have more tumors than A and R rats.

*Growth and lifespan.* — Correlation coefficients between lifespan, relative growth rate, predicted mature body weight, actual maximum body weight, youngest age of attaining maximum body weight, and the ratio of maximum body weight to youngest age of attaining maximum body weight are shown in Table 6. Predicted mature body weight was associated negatively and significantly with longevity only in R animals. Relative growth rate was not related significantly to longevity, regardless of dietary treatment. Actual maximum body weight was correlated positively with survival only in A rats. Youngest age of attaining maximum weight was associated positively with survival in rats fed ad libitum during the second year of life (A and RA), whereas the ratio of maximum weight to youngest age of attaining maximum weight was correlated negatively with life span in these same groups.

## DISCUSSION

The decreased relative growth rate and body weight and increased life span observed for rats

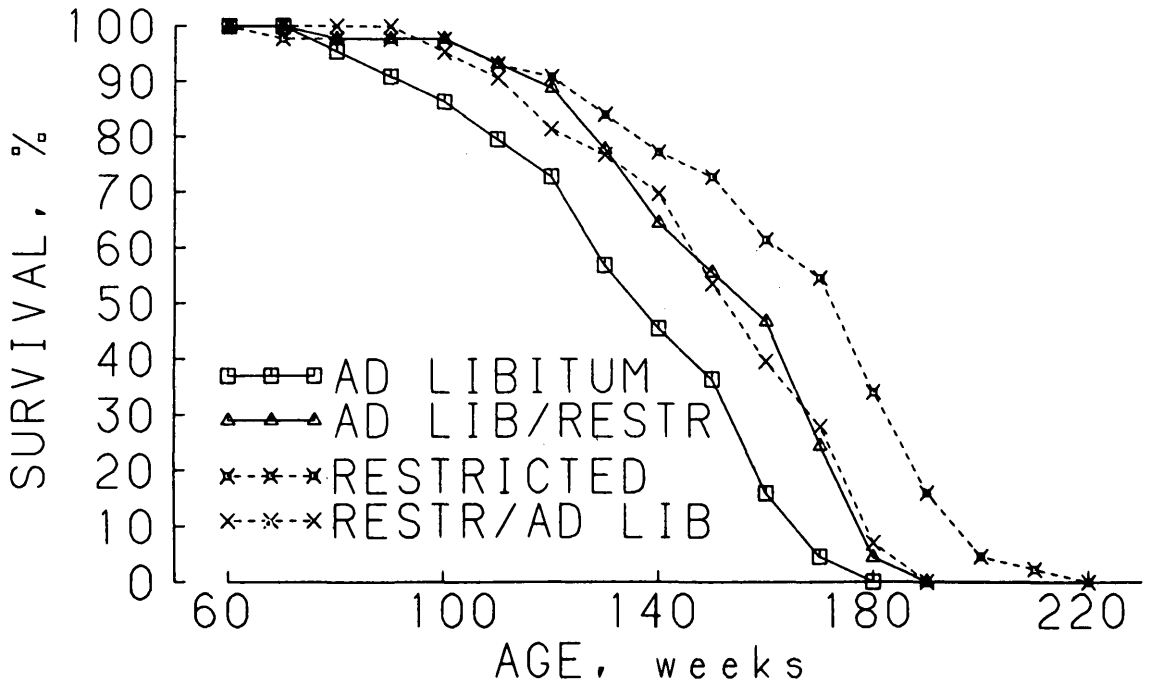


Figure 1. Survival curves of rats fed lab chow either ad libitum throughout life (AD LIBITUM); ad libitum until 1 year of age and restricted thereafter (AD LIBITUM-RESTRICTED); restricted until 1 year of age and ad libitum thereafter (RESTRICTED-AD LIBITUM); or restricted throughout life (RESTRICTED).

restricted from weaning agree with the results of Yu et al. (1982). Rats transferred from ad libitum to restricted feeding at 1 year of age lost body weight subsequently. Alternatively, rats transferred from restricted to ad libitum feeding at 1 year of age gained body weight.

Although at 1 year of age restricted animals had smaller absolute amounts of body fat, protein, ash, and moisture, their relative body compositions did not differ from those of rats fed ad libitum. These data are consistent with the *compositional homeostasis* theory of Weil and Wallace (1963), which proposed that restricted animals develop smaller bodies of relative composition similar to those fed ad libitum. At 2 years of age, A rats had markedly greater percentages of body fat than R animals. The increases in body fat during the second year of life of A rats accounted for more than 50% of their weight gain. In agreement with the results of others (Lesser et al., 1973, 1980; Yu et al., 1982), absolute amounts of body protein of A rats did not change from 1 to 2 years of age.

At 2 years of age rats restricted during the first year of life and fed ad libitum during the second had higher absolute amounts of all body constituents than restricted rats at 1 year of age. Thus, in a pattern similar to that observed by Nolen (1972), RA rats appeared to catch up and at 2 years of age exhibited a relative body composition no different from that of animals fed ad libitum from weaning. Similarly, rats fed ad libitum until 1 year of age and then restricted until 2 years of age (AR) had a mean relative body composition the same, except for ash, as that of animals restricted until 2 years of age.

In the present study rats fed restricted diets throughout life survived longer than those restricted until adulthood and fed ad libitum thereafter (RA) or those to which the reverse feeding regimen was administered (AR). Both AR and RA rats lived longer than the controls fed ad libitum. Our results support other work (Weindruch & Walford, 1982), which has shown that dietary restriction of mice initiated at 1 year of age increases life span. As suggested by Goodrick et al. (1983), the beneficial effect of dietary restriction appears to decline as the age at the time of its introduction is increased. The observation that rats fed ad libitum until 1 year of age and restricted thereafter lived as long as those administered the reverse dietary regimen and significantly longer than those fed ad libitum throughout life may be applicable to humans (e.g., an AR-type feeding pattern allows maximal skeletal and lean tissue growth along with the possibility of life span enhancement).

The significant positive correlation found in the present study between actual maximum body weight and longevity of rats fed ad libitum is consistent with the findings of Goodrick et al. (1982, 1983) and Ingram et al. (1982). In addition, our studies revealed that the youngest age at which A and RA rats attained their maximum body weight was correlated positively with longevity. Thus, in these animals, the accumulation of body mass, including fat, over an extended period of time was consistent with longevity. A nonsignificant rela-

Table 5. Effect of Feed Restriction on Mean and Maximum Life Spans of Rats

| Group | Mean life span (weeks) | Maximum life span[a] (weeks) |
|---|---|---|
| Ad libitum | 133.1 ± 4.1[C] | 169.4 ± 1.9[C] |
| Restricted | 163.4 ± 3.9[A] | 200.1 ± 3.1[A] |
| Ad libitum/restricted | 150.0 ± 4.6[B] | 178.6 ± 1.5[B] |
| Restricted/ad libitum | 149.2 ± 3.6[B] | 182.6 ± 2.1[B] |

*Note.* Values are means plus or minus the standard errors of the means; values in a column not sharing a common superscript are significantly different from each other ($p < .05$).

[a]Mean survival time for longest lived 10% of each population.

Table 6. Correlation Coefficients Between Life Span and Growth Parameters of Longevity Animals by Dietary Group

| Group | Predicted mature body weight[a] | Relative growth rate[b] | Actual maximum body weight | Youngest age maximum body weight attained | Maximum body weight + youngest age maximum body weight attained |
|---|---|---|---|---|---|
| Ad libitum | 0.06 | 0.20 | 0.30* | 0.64** | −0.53** |
| Restricted | −0.33* | 0.23 | −0.25 | 0.21 | −0.29 |
| Ad libitum/restricted | −0.28 | −0.06 | −0.25 | 0.06 | −0.24 |
| Restricted/ad libitum | −0.21 | −0.06 | −0.13 | 0.67** | −0.57** |

[a]Predicted mature body weight = A in Brody (1964) equation.

[b]Relative growth rate = k in Brody (1964) equation.

*$p < .05$. **$p < .001$.

tionship between maximum body weight and longevity was observed by Ross et al. (1976) in rats fed ad libitum. They reported that several other growth parameters could be used to predict longevity. In our studies relative growth rate was not correlated significantly with longevity in any group of animals, and predicted mature body weight was correlated significantly with longevity only in restricted animals. The absence of significant relationships between relative growth rates and longevity agrees with the findings of Ingram et al. (1982).

Although body weights of R rats were lower than those of A animals, no delay in attainment of maximum body weight was observed; yet the mean life span of R rats was 30 weeks longer than that of A rats. In contrast with observations in A rats, neither maximum body weight nor the age at which it was attained was related significantly to longevity in R rats. The correlation coefficients between life span and maximum body weight in A ($r = +.30$) and $R$ ($r = -.25$) groups were approximately equal numerically but opposite in sign; these coefficients approximate the values and signs of those of RA and AR groups, respectively. The life spans of RA and AR rats, however, were equal and intermediate to those of R and A animals. The inability of the Brody growth equation to predict maximum body weights of rats fed ad libitum after 1 year of age (A, RA) was related to the large gains in body weight and fat by these animals during the second year of life. In animals restricted after 1 year of age (R, AR), predicted weight agreed with maximum body weight quite well. These observations relate to why the correlation coefficients between life span and either predicted or maximum body weight of rats restricted after 1 year of age agree with each other, whereas those calculated for rats fed ad libitum after 1 year of age did not agree with one another.

Thus, although intermittent feeding imposed at weaning or after cessation of growth and development lengthened life span, neither growth parameters nor body composition data related consistently to the life-prolonging effect. The importance of low body weight to longevity is indicated by the long mean life span of R animals and the negative correlations between longevity and predicted mature and actual maximum body weights of these animals. Conversely, the relevance of high body weight to longevity is indicated by the relatively short mean life span of A rats but positive correlation between their actual maximum body weights and longevity. It is obvious that body weight and/or the process of gaining it is related to longevity in contrasting ways in restricted- and ad libitum-fed animals. This study and others (Goodrick et al., 1982, 1983; Ingram et al., 1982) indicate significant relationships between body weight and/or growth indices and longevity. On the other hand, the increased longevity observed in animals fed ad libitum the first year of life and restricted thereafter de-emphasizes the relevance of classic theories that necessitate growth retardation for increased longevity. A delay in the onset of morbidity and/or the decline of one or more physiological systems (e.g., the immune or renal systems) may explain the life-lengthening effect of restricted feeding during adulthood. Additional study of the relationships between dietary regimens known to be life-prolonging and physiological systems that exhibit age-associated decrements is warranted.

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Received August 31, 1984
Accepted July 12, 1985